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A DECADE OF ANTI-INFLAMMATORY STEROIDS, FROM CORTISONE TO DEXAMETHASONE

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* This series of papers is the result of a conference on *A Decade of Anti-Inflammatory Steroids, from Cortisone to Dexamethasone* held and supported conjointly by The New York Academy of Sciences; Merck Sharp & Dohme Research Laboratories, Rahway, N. J., and West Point, Pa.; and Schering Corporation, Bloomfield, N. J., on December 15 and 16, 1958.

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INTRODUCTORY REMARKS

Albert S. Gordon
Department of Biology, Graduate School of Arts and Science,
New York University, New York, N. Y.

Few classes of compounds have received the detailed attention given to the steroids of glandular origin. This is especially true of the adrenocorticosteroids. Great energy has been expended in the fractionation, crystallization, and eventual synthesis of these substances; and rightly so, for the availability of the pure steroids has not only permitted a more penetrating and reliable analysis of the role of the endocrines in body metabolism, but has added significantly to the armamentarium available for the treatment of a variety of disease states in man, particularly those that are inflammatory in nature.

When the natural steroids were first being characterized, their potent effects on biological processes appeared to indicate that they were compounds possessed of the highest order of activity, upon which man could not further improve. Recent years have seen a striking refutation of this original supposition; not only has the resourceful chemist fabricated steroids of greater biological activity, but he has molded them in such a way as to amplify their desirable effects and to dampen those that would act as deterrents to their continued successful use as therapeutic agents.

The introduction of halogens (particularly fluorine in the 9-alpha position), the delta-1 derivatives, and the 6-methyl and 16-hydroxy derivatives of the basic corticosteroids, have enabled these advances to be made. The 16-alpha methylation effect, when combined with the delta-1 and 9-alpha fluoride configurations, has produced a most interesting and promising therapeutic steroid: dexamethasone.

Although the importance of the synthetic derivatives of the basic corticosteroids cannot be denied, let us not lose sight of the fact that the adrenal gland, in its operations within the organism, produces and releases not a single steroid, but a multiplicity of them, each capable of somewhat different biological activities. This mixture of steroids, elaborated under normal conditions and increased under conditions of stress, is an evolutionary heritage, time-tested by the forces of natural selection and acting to protect the individual against the rigors of the environment. It seems possible that there are as yet undisclosed additive, synergistic, and antagonistic actions occurring among these steroids, geared primarily for the maintenance of homeostasis and not achievable by any single steroid, regardless of the degree to which its biological activities may have been enhanced. Further contemplation and work along these lines is most important.

INTRODUCTION

Edward C. Kendall
Princeton University, Princeton, N. J.

In 1948 The New York Academy of Sciences published a monograph[1] on the same subject as this, to which I also contributed. A comparison of the titles of the papers published then and now indicates the extent of the progress that has been made in the investigation of the adrenal cortex in the intervening decade.

One of the most striking differences is the availability of material. In 1947 the only source of the cortical hormone designated Compound E was the adrenal gland. It could not be purchased, and it was prepared in only three places. I have a letter from the late J. B. Murphy in which he requested 6 mg. of the hormone for some experiments on leukemia in mice. Such a request from a scientist in the first rank, on a subject as important as leukemia, called for generous consideration; I sent him 60 mg.

This type of work, although limited to animals, nevertheless slowly accumulated data that indicated the importance of the adrenal cortex.

Meanwhile, the firm of Merck & Co., Inc., Rahway, N. J., became interested in the production of these compounds for use in clinical medicine. There was no assurance that the project would be worthwhile, but the firm began an exploration of methods for the large-scale production of compounds A and E, dehydrocorticosterone and cortisone, respectively. A method for the preparation of Compound A from bile acids was devised in my laboratory in 1944 and, soon afterward Merck enlarged this procedure and made available a sample of this hormone.

Compound A was found to be without value for treatment of Addison's disease. This was discouraging, but still the firm persisted. In 1946 L. H. Sarett, in the Merck laboratory, synthesized Compound E for the first time by rearrangement of another steroid. This was important, for it was convincing proof that the hormone could be prepared. It was not the full answer, however, because the method employed could not be used for large-scale production.

During the summer of 1948 a method was devised by which Compound E could be prepared. Essential contributions were made both by L. H. Sarett and by my laboratory. A small amount of this cortical hormone was available, but the failure of Compound A had created misgivings, and very few clinicians were interested in the investigation of a compound for which the only obvious application was Addison's disease.

Ten years ago the team of Hench, Slocumb, Polley, and Kendall at the Mayo Clinic, Rochester, Minn. used Compound E, for the first time in clinical medicine, for the relief of rheumatoid arthritis. Announcement of the results was made in April 1949 and, almost over night, this hormone, now designated cortisone, was shown to be effective in more than 100 clinical syndromes; cortisone was used and abused without limit.

From this world-wide investigation two conclusions became obvious. There was a place for cortisone and its companion hydrocortisone in clinical medicine, but production of undesirable side reactions suggested the possibility that modification of the chemical structure might enhance the desired clinical result and decrease the objectionable side effects.

The first question was concerned with the other closely related hormones, Compounds A and B. These were found to be without value. Moreover, the first modifications of cortisone were less active than the original hormones. However, the stakes were high, competition was keen, and the number of laboratories entering the field increased rapidly. This onslaught of able organic chemists has produced a virtual museum of relatives of cortisone.

The physiological effects of these new compounds comprise a new chapter in pharmacology. One immediate consequence has been the necessity of devising a method by which the new compounds can be screened before they are given to patients.

This monograph will bring our knowledge regarding these several aspects up to date. The new man-made steroids have provided a basis for the correlation of physiological activity and chemical structure. It has been necessary to develop this relationship *de novo*. The plethora of new compounds has shortened the time required, and also has expanded the scope of our knowledge. This is research that all scientists will recognize as fundamental.

At the same time, the application of the new steroids in the field of clinical medicine has enlarged our armamentarium with new and valuable tools. A few years ago a former associate informed me that I had provided jobs for more men than anyone ever had; if the corticosteroid family continues to grow, this may yet become true.

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Part I. Biochemical Studies

SOME ASPECTS OF THE EVOLUTION OF ANTI-INFLAMMATORY STEROIDS

Lewis H. Sarett
Merck Sharp & Dohme Research Laboratories Division of Merck & Co., Inc., Rahway, N. J.

The synthesis of the anti-inflammatory steroid dexamethasone, 16α-methyl-9α-fluoroprednisolone (Decadron*) was carried out in the Research Laboratories Division of Merck & Co., Inc., Rahway, N. J., by G. E. Arth and his associates.[1] The synthetic route was a modified adaptation of previously described procedures for introduction of the required functionality in the A-ring, the C-ring, and the side chain, augmented, however, by the addition of an α-methyl group at C-16.[2] The presence of this methyl group gives rise to increased steric hindrance at C-20; hindrance that, on the one hand, impedes chemical introduction of the C-17 hydroxyl group, but eventually confers on the side chain an increased degree of biological stability.[3]

The details of our synthetic work will not be related here since, in any case, Eugene Oliveto, elsewhere in this monograph, will describe corresponding studies carried out by his associates. Instead, it may be pertinent on this occasion to review a different aspect of anti-inflammatory steroids, one that has commanded the vigilant interest of many, if not all, United States pharmaceutical research organizations. This aspect is the *design* of anti-inflammatory steroids. Behind each steroid that has been carried through to synthetic completion there has been an idea, sometimes an incorrect one, without which the attendant synthetic effort would not have been undertaken. It is the development of some of these ideas during the past decade to which I now address myself.†

During the first years following the discovery of cortisone by Hench, Slocumb, Polley, and Kendall in 1948, investigation of the synthesis of structural modifications began slowly. There were several good reasons for this. First, cortisone was a natural product, and one of the dominant trends of thought of the period immediately preceding its advent had been the conviction of the superiority of natural products. The vitamins had been discovered and synthesized; each had filled perfectly its role of replacement in deficiency diseases without the necessity of man-made synthetic modifications. The prevailing attitude was: what was made by Nature is necessary and sufficient. Second, the steroid chemists qualified to synthesize new modifications of cortisone were occupied for the most part with a more urgent problem; that of developing the elaborate and inefficient laboratory synthesis of cortisone to a point suitable for large-scale manufacture. Finally, all the synthetic analogues that did result from research on manufacturing processes were of diminished anti-inflammatory activity.

One of the earliest examples is illustrative of the course of the search for better processes. In the course of efforts to find more satisfactory means of introducing the Δ^4-3-keto group, Mattox and Kendall[8] came upon an undesired by-product of oxidation of an intermediate dinitrophenyl hydrazone. The by-product, 6-dehydrocortisone, was suspected of producing unwanted biological effects but, on testing, proved to be only a weaker and somewhat more salt-retaining version of cortisone.[9]

---

* Merck Sharp & Dohme Division of Merck & Co., Inc., Philadelphia, Pa.

† Detailed treatments of the various phases of this subject are available.[4–7]

The process intermediate $3\alpha,17\alpha$,21-trihydroxy-11,20-diketopregnane was tested and found inactive in the mouse. Its epimer at C-5, a reduction product of cortisone, was similarly inactive. The Δ^1 isomer of cortisone was synthesized by Wilson and Tishler[10] and provided only a small fraction of the activity of the Δ^4 isomer.

During these early years the only advance in potency was that achieved through synthesis of hydrocortisone by Wendler *et al.*[11] in 1950. However, hydrocortisone was, after all, a natural product, and served, if anything, to confirm chemists in their thinking that the secretions of the adrenal gland were in all ways more useful than anything likely to be devised by the steroid chemist.

In 1953 this view was modified by the finding of Fried and Sabo[12] that 9α-chlorohydrocortisone was more potent than the adrenal hormones. The 9α-chloro compound was a decidedly unnatural modification of the steroid hormones, but owed its origin to interest on the part of its discoverers in finding a new route to hydrocortisone from an intermediate available by microbiological fermentation. A 9,11-bromhydrin, in which the bromine atom was of doubtful configuration, was submitted to bioassay as a means of obtaining confirmatory evidence on configuration. It was biologically active, as was the corresponding chlorohydrin, the latter in fact being the most potent anti-inflammatory steroid found to that time. In 1954 9-fluorohydrocortisone was described by Fried and Sabo.[13] Its synthesis followed as an extension of the greater activity of the 9α-chloro analogue over the bromo. The subsequent synthesis of 12α-halo analogues of corticosterone,[14, 15] and the finding that their activity was comparable to that of the 9α-isomers resulted from Fried's speculation that the activity enhancement of the 9-halogen was due to its acid-strengthening effect on the 11β-hydroxyl group.[16]

The following year witnessed a landmark, the synthesis of prednisone, the first systemically useful anti-inflammatory steroid since cortisone and hydrocortisone.[17] This steroid arose as a by-product of a bacterial hydrolysis of a C-11-acetate, but its more or less fortuitous beginnings in no way limited its clinical success. Aided by its reduced propensity for salt retention, it expanded the useful application of corticosteroids in several directions.

The discovery was made in 1955 that functional groups that enhanced anti-inflammatory activity in themselves could be combined within the same hydrocortisone nucleus in a roughly additive way. With the recognition that the Δ^1 bond and the 9-fluorine atom individually enhanced activity, the compound combining these functions, Δ^1-9α-fluorohydrocortisone, was made available for clinical screening by no fewer than 5 pharmaceutical research groups in 1955.[18-22] Although its clinical potency was even greater than that of 9-fluorohydrocortisone, it shared with the other 9-halosteroids known at that time the unhappy property of rapidly producing edema and kaluresis.[23]

The existence of the 9α-fluoro group, with its potential for enhancing anti-inflammatory activity, furnished impetus for a new research current—the search for a group that could be added to the steroid nucleus (or subtracted from it) and that would cancel the salt-retaining properties of the 9-halogen. One of the earliest logical attempts was that of Fried, who synthesized the 21-desoxy analogue of 9-fluorohydrocortisone.[24] The 21-hydroxyl group was implicated in salt retention, since conversion of desoxycorticosterone acetate (DOCA) to progesterone proceeded from a greater to a lesser salt-retaining substance with loss of the 21-OH. In the case of 21-desoxy-9-fluorohydrocortisone, this expectation was realized but, unfortunately, this modification was only weakly active as an anti-inflammatory steroid in experimental animals.[25]

In spite of early failure, efforts to utilize the 9α-halogens continued. With the advent of triamcinolone, synthesized by Bernstein and his associates in 1956,[26] these efforts met their first success. In the presence of the 16α-hydroxyl group, the position of which was selected on the basis of its being one at which hydroxylation occurred in normal mammalian metabolism, the 9α-fluorine no longer retained salt. This desired effect was not achieved without cost, however, since anti-inflammatory potency was also cut back by the 16α-hydroxyl. In terms of potency, the 16α-hydroxyl nearly cancelled the seven- to tenfold enhancing power of the 9α-fluorine.

Parallel to the unfolding of the 9-fluorine story, synthetic work began on another family of activity-enhancing groups: the nuclear methyls. Again the influence of research toward new manufacturing processes could be discerned. Synthetic intermediates suitable for bromination at C-2 are the 2-oxalyl-3-keto-4-pregnenes. These intermediates were aimed at providing access to new routes to prednisone but, at the same time, could alternatively be methylated at C-2, as well as brominated. Accordingly, Hogg and his associates reported 2α-methylhydrocortisone in 1955.[27] Despite a striking increase in anti-inflammatory activity over the nonmethylated analogues, the 2α-methylcorticoids were salt retainers comparable with DOCA, 2α-methyl-9α-fluorohydrocortisone being even more potent than aldosterone. Aided by studies showing that the 2α-methyl group provided stabilization against the 4,5-reductases of the liver,[28] the Upjohn group* continued work on methylated steroids and, in 1956, published a report of the 6α-methylsteroids.[29] These substances proved to be nearly comparable to the 2α-methylsteroids in enhancing anti-inflammatory potency, but lacked the undesirable electrolyte effects. Accordingly, 6α-methylprednisolone was made available clinically. In spite of the usefulness of the 6α-methyl group in conjunction with the prednisolone nucleus, 6α-methyl-9α-fluoroprednisolone never appeared clinically as an anti-inflammatory agent. It remained for the discovery of the 16α-methylcorticosteroids to disclose that it was possible to obtain a functional group that enhanced anti-inflammatory potency and, at the same time, promoted freedom from salt retention. This group of compounds owed its genesis in the Merck laboratories to an interest in anesthetic steroids.[30] When administered intravenously to dogs, 3α-hydroxy-11,20-diketopregnane has anesthetic properties,[31] and it seemed possible that a 16α-methyl group could intensify this activity. Although this did not prove to be the case, the product synthesized provided an attractive intermediate for further elaboration into 16α-methylprednisolone and, with the discovery of the granuloma-inhibiting effect of the latter, synthesis of the remaining members of the series.

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* The Upjohn Company, Kalamazoo, Mich.

Most recently the interesting 16β-methyl series has been described.[32, 33] It has the distinction of being the first active glucocorticoid with a β-substituent, and resembles the α-epimer both in potency and in freedom from salt retention.

As the methylated steroids were explored, so too were their fluorinated counterparts. As rationales for success, the examples of the 9α- and 12α-halogens, with their inductive effect on C-11, prompted speculation on the possible properties of C-21- and C-6-halogenated steroids, which similarly would have decreased electron densities, although on the carbonyl function at C-20 and C-3, respectively. During 1958 and early 1959 several publications appeared describing 6-fluoro[34, 35] and 6-chloro[36] analogues of hydrocortisone. In contrast to the decreased activity produced by halogen at C-21,[37, 38] the 6α-fluoro and 6α-chloro derivatives showed enhanced potency comparable with that of the 6α-methyl analogues.

The tangible achievements in the field of new anti-inflammatory steroids during the past decade—biologically speaking—can be summarized by a table of functional groups. These would comprise the 8 structural elements known to enhance anti-inflammatory activity when present in the hydrocortisone molecule. They are the 2α-, 6α-, 16α-, and 16β-methyl groups; the 6α-, 9α-, and 12α-fluorine atoms; the Δ^1 bond and the 9α-chlorine atom. The effects of most of these have been nicely quantitated by Fried and Borman.[39] In addition to those groups that enhance activity, there are those that modify it in a clinically useful way. To date, this effect is limited to repression of salt retention and is found principally in the 16α-hydroxyl, and the 6α-, 16α-, and 16β-methyl and 6α-chloro functions.

The existence of these structural modifications of hydrocortisone, with their broadly similar anti-inflammatory properties, has led to strenuous endeavors toward unification and understanding both in biological and chemical terms. The search for a common mechanism of action at the enzyme level has stimulated considerable work, but the problem is still largely unsolved.[40] In chemical terms, the receptor site for hydrocortisone and its analogues is still to be visualized only in terms of the molecules that fit it, since no independent system for measurement is available. It is feasible, however, for the organic chemist to address himself to the problem of the geometry of the hypothetical receptor site for hydrocortisone within these immanent limitations.

The basic postulates required for construction of a model of the molecular receptor site for the anti-inflammatory steroids are:

(1) That there be a single type of molecular site with identical functionality and geometry situated in those tissues where anti-inflammatory steroids can be seen grossly to counteract inflammation. This is, of course, no more than an extension of Ehrlich's classic postulate that biological activity is the result of the interaction of a drug with a particular category of receptors.

(2) That the receptor site be complementary to part of the anti-inflammatory molecule. This assumption rests on the idea of closeness of fit between drug and receptor. The high degree of structural specificity involved in enzyme and substrate binding and in antigen-antibody interactions lends credence to this view. Since the forces available for binding neutral molecules together

(dipole-dipole, dipole-induced dipole, hydrogen bonding, and van der Waal's attractions) are short-range and fall off rapidly with distance, a close surface-to-surface fit appears logical.

Proceeding from these assumptions, one may map the imaginary complement of the anti-inflammatory steroids. Similar processes of visualization have been carried out for the acetylcholinesterase receptor site by Nachmansohn and Wilson,[41] for the analgesic receptor site by Beckett *et al.*,[42] and for α- and β-steroid dehydrogenases by Marcus and Talalay.[43]

Since hydrocortisone is the prototype of the anti-inflammatory steroids, it can serve as the simplest model on which to construct a complementary surface. Consideration of the conformational representation of this molecule shows that 2 of the 3 functional groups essential for anti-inflammatory activity* —the 11β-hydroxy and the acetyl side chain—project above the plane of the nucleus. Since it would seem necessary that the three essential functional groups interact with corresponding points in the receptor site, the fit between steroid and receptor would be one involving C-3=O, C-11β-OH, and C-17-$COCH_2OH$. This would correspond to a β- or top-side absorption. It is noteworthy that the ingenious concept of I. E. Bush[45] (that hydrocortisone may function as a coenzyme by donating the 11α-hydrogen as hydride ion) would be in seeming conflict with simple β-side binding. Furthermore, since both a 3-keto group and 11β-hydroxyl are essential for anti-inflammatory activity, binding with these specific groups (and not, for example, with an 11-ketone) is required. In the case of the side chain, C-17- and C-21-desoxy analogues of hydrocortisone are known that possess anti-inflammatory activity, whereas compounds lacking the C-20-carbonyl do not.[46] Accordingly, the receptor site can be visualized as binding to 3 points: C-3, C-11, and C-20, and as fitting that surface of the hydrocortisone molecule where these groups are located.

The usefulness of this representation depends on how well it conforms with experience. In particular, known structural modifications of hydrocortisone that retain anti-inflammatory activity must have a molecular geometry consistent with the hypothetical receptor site. It is obvious that modifications of hydrocortisone with α-axial (or bottom-side) substituents should be perfectly capable of the hypothecated top-side interaction with the receptor site. The anti-inflammatory activity of the 7α-methyl,[47] 9α-halo, 9α-methyl,[48] 12α-halo, and 14α-hydroxy[49] analogues of the anti-inflammatory steroids support this view. Equatorial substituents such as 2α-methyl,[50] 6α-methyl, and 6α-halo, lying in the general plane of the nucleus, similarly should allow of top-surface combination. The axial 6β substituents should not, however, and it is reasonable to find that they are inactive compared with their α epimers. The active 16α substituents are similarly disposed on the α side. The interesting 16β epimers indubitably are top-side substituents and could have been expected to interfere with a surface-to-surface fit. The fact that they do not could be a reflection of their oblique angle relative to the plane of the nucleus, or of incompleteness of surface-to-surface fit.

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* As measured by the granuloma assay of Meier *et al.*[44] The data to support the generalizations regarding the dispensability of the C-17 and C-21 hydroxyl functions in hydrocortisone modifications are based on assay results of Silber, Stoerk, and Winter of the Merck Institute and also on those of Fried and Borman.[7]

The model of three-point, top-side binding constructed in this fashion is, at the very least, a convenient device for remembering the configurations of the active anti-inflammatory steroids. At best, it corresponds in some degree to a reality that remains to be delineated.

In terms of medical goals remaining to be studied, it is pertinent to inquire whether independent receptor sites exist for calcium loss and the other undesired effects that can accompany steroid therapy. If they do, what is their molecular architecture and how can advantage be taken of it to achieve practical medical advantages? It is to be hoped that steroid chemistry will be as well equipped to decipher these subtle problems as it has been to resolve the apparently simpler ones of increasing anti-inflammatory potency and dissociating salt retention.

Acknowledgment

I gratefully acknowledge the assistance of Miss Frances Hoffman in the preparation of this manuscript.

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SYNTHESIS OF 16α- AND 16β-METHYL CORTICOIDS

Eugene P. Oliveto
Schering Corporation, Bloomfield, N. J.

The search for better corticoids involves, for the most part, introduction of functional groups into known anti-inflammatory steroids in the hope of diminishing or eliminating the unwanted and undesirable effects that have no bearing on the anti-inflammatory action. A secondary aim is to increase potency, but this is justified only if there is no corresponding increase in side effects, so that the ultimate aim is really the same: namely, separation of responses and an increase in the therapeutic ratio.

Despite attempts to inject some rationale into corticoid research, there is still more art than science in deciding which functional groups to introduce and at what point in the molecule to place them.

There are by now many examples of corticoids that have been modified by the addition of a methyl group at various points in the molecules.[1-5] These added groups have had unpredictable and variable effects on the activity of the parent corticoid, ranging from complete loss of activity to a marked increase in salt- and water-retaining effects. Thus, there was no way of knowing in advance what the properties of 16-methyl-substituted corticoids would be.

Actually, the key reactions for introduction of methyl groups at C-16 had been discovered in 1942 by Marker and Crooks[6] for 16α-methyl (FIGURE 1) and, in 1944, by Wettstein[7] for 16β-methyl (FIGURE 2). With this pioneer work as a background, the next logical step toward the preparation of 16-methyl corticoids is choice of the proper starting steroid.

It is an interesting side light that both Merck* and Schering used not only the same raw material but also, essentially, the same synthesis for the preparation of both 16α-methylprednisone and 16β-methylprednisone.[8-10] The raw material is desoxycholic acid, which is converted to 3α-acetoxypregnane-11,20-dione in about a 15-step synthesis. A Δ^{16} double bond is then introduced, either by direct bromination-dehydrobromination, or by first preparing the enol acetate and following with brominating-dehydrobrominating (FIGURE 3). The 16β-methyl group can then be introduced by the Wettstein procedure (FIGURE 4) and the remainder of the synthesis to 16β-methylprednisone completed by standard procedures: (1) introduction of the 17α-hydroxy by enol acetylation, peroxidation, and hydrolysis; (2) introduction of the 21-acetoxyl by bromination, followed by reaction with potassium acetate; (3) oxidation of the 3-hydroxyl to ketone with chromium trioxide or *N*-bromosuccinimide; and (4) dibromination at C-2 and C-4, followed by dehydrobromination with collidine or dimethylformamide to produce 16β-methylprednisone acetate. The 21-acetate may then be hydrolyzed to alcohol with either acid or alkali, to yield 16β-methylprednisone (FIGURES 5 and 6).

To prepare the 9α-halo analogues, an intermediate from the above synthesis, 16β-methyl-3α,17α-dihydroxypregnane-11,20-dione, is reacted with ethylene glycol and an acid catalyst to form a 20-monoethylene ketal, the 11-ketone is

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* Merck & Co., Inc., Philadelphia, Pa.

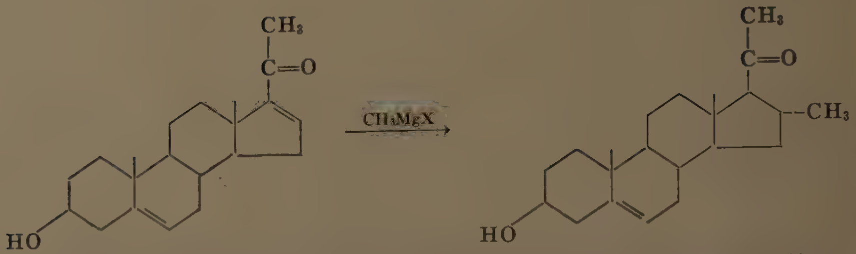


FIGURE 1. Reaction for 16α-methyl, discovered by Marker and Crooks in 1942.

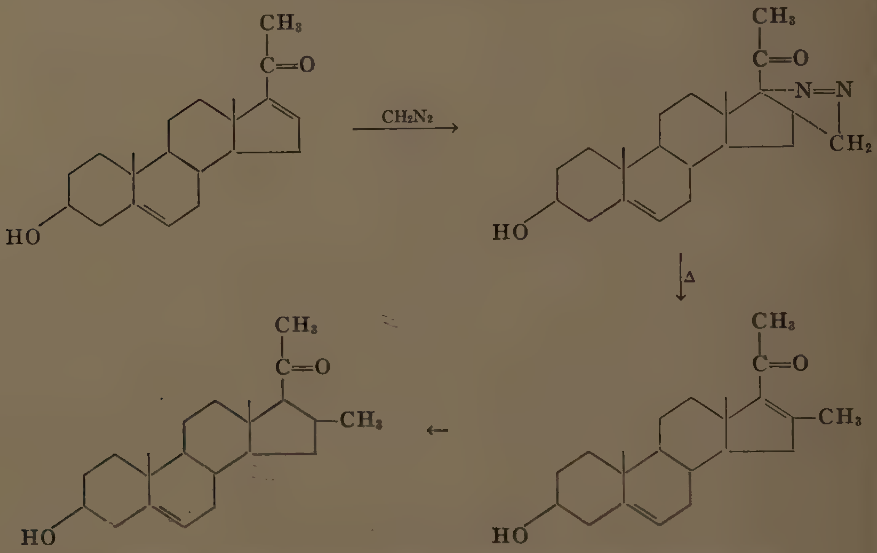


FIGURE 2. Reaction for 16β-methyl, discovered by Wettstein in 1944.

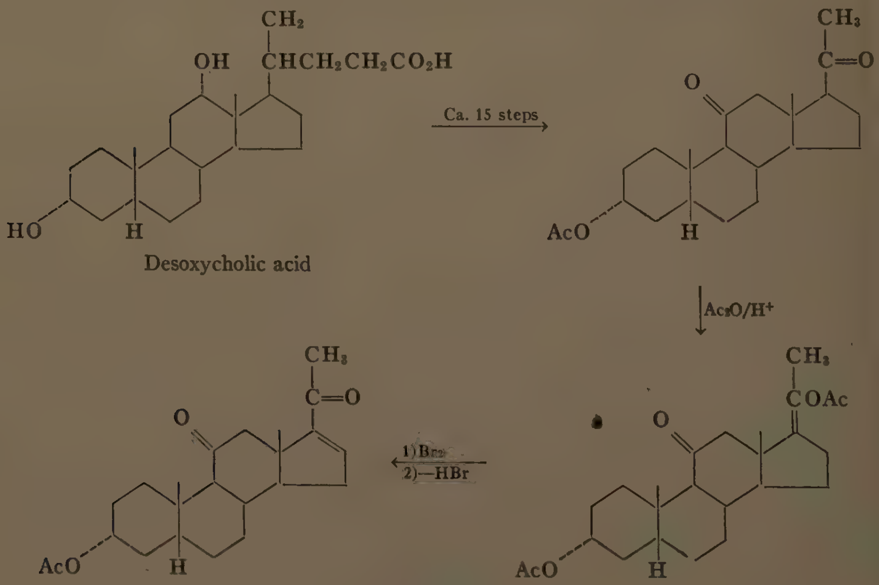


FIGURE 3.

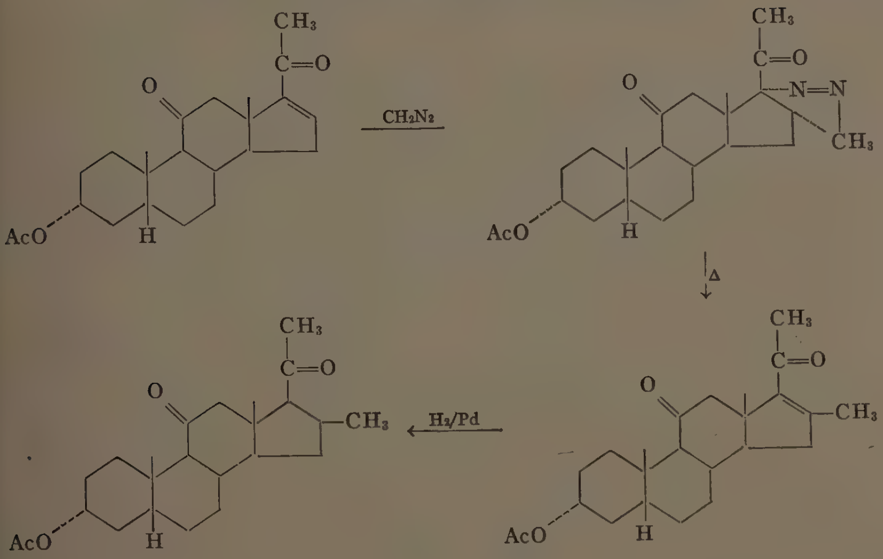


FIGURE 4.

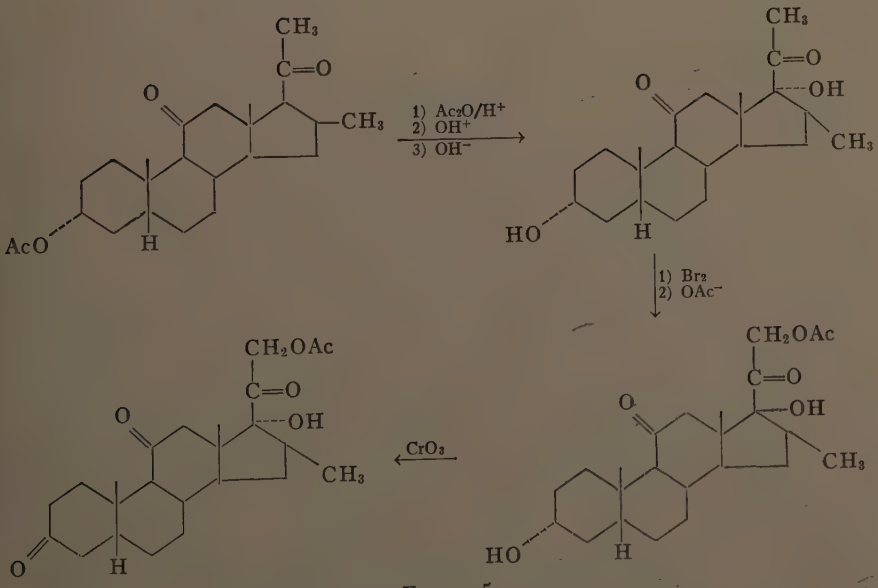
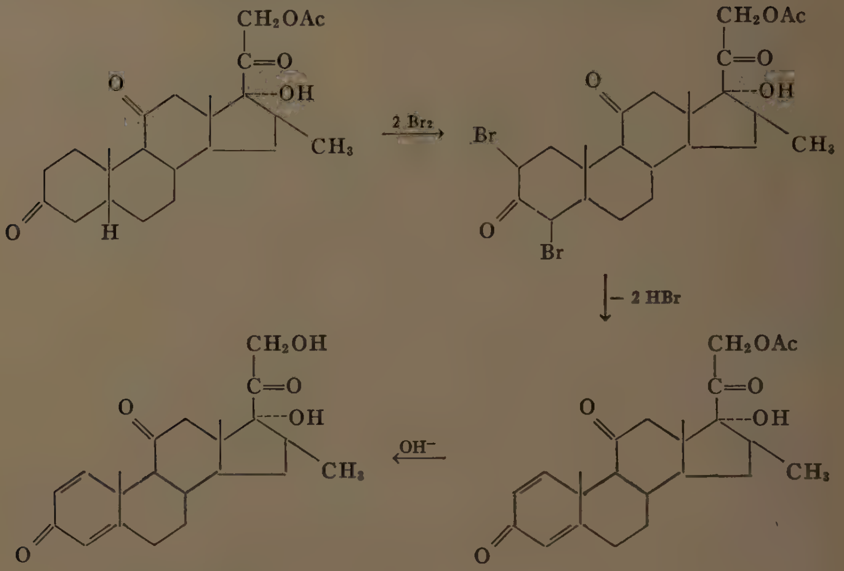


FIGURE 5.



16β-Methylprednisone

FIGURE 6.

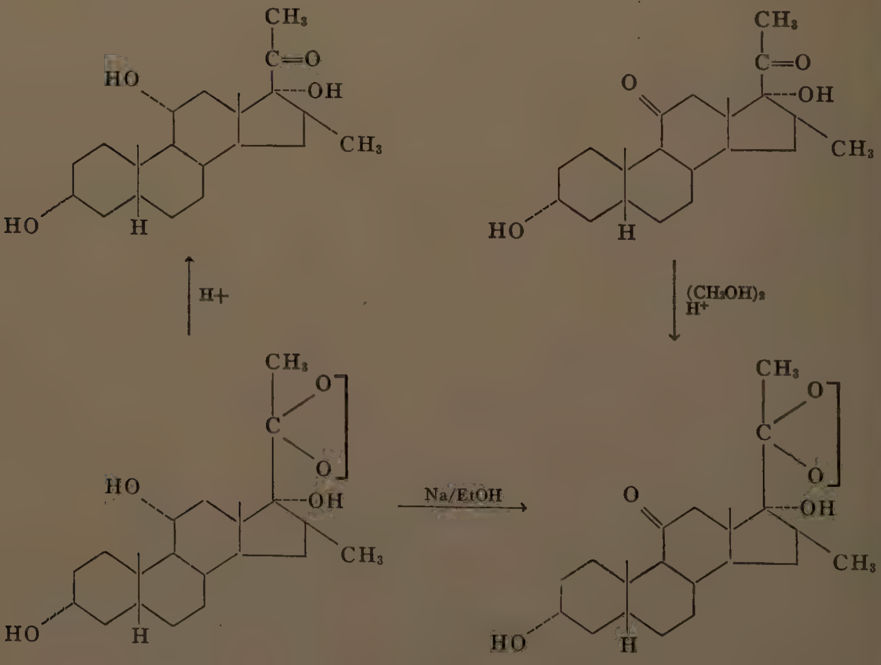


FIGURE 7.

reduced with sodium and alcohol to an 11α-hydroxyl, and the protecting ketal grouping is removed by acid hydrolysis (FIGURE 7). The 21-acetoxyl is introduced in the usual fashion, and a selective oxidation with *N*-bromosuccinimide produces 21-acetoxy-11α,17α-dihydroxy-16β-methylpregnan-20-one (FIGURE 8). Two double bonds are introduced into the A-ring by bromination-dehydrobromination, the 11α-hydroxyl is reacted with methansulfonyl chloride in pyridine to form the 11α-mesylate, and this group is then eliminated by treatment with sodium acetate to form a $\Delta^{9(11)}$ double bond. This is then reacted with hypobromous acid to form a 9α-bromo-11β-hydroxy compound.

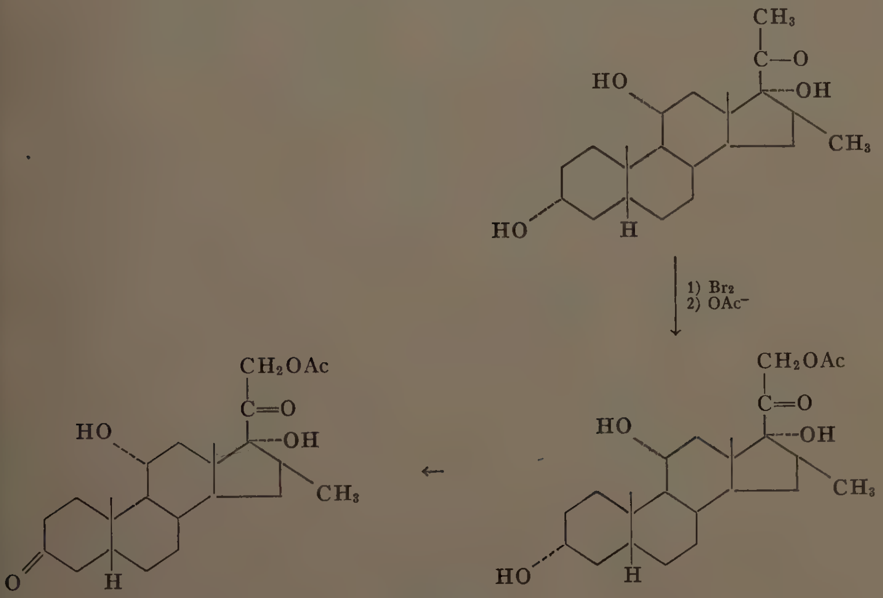
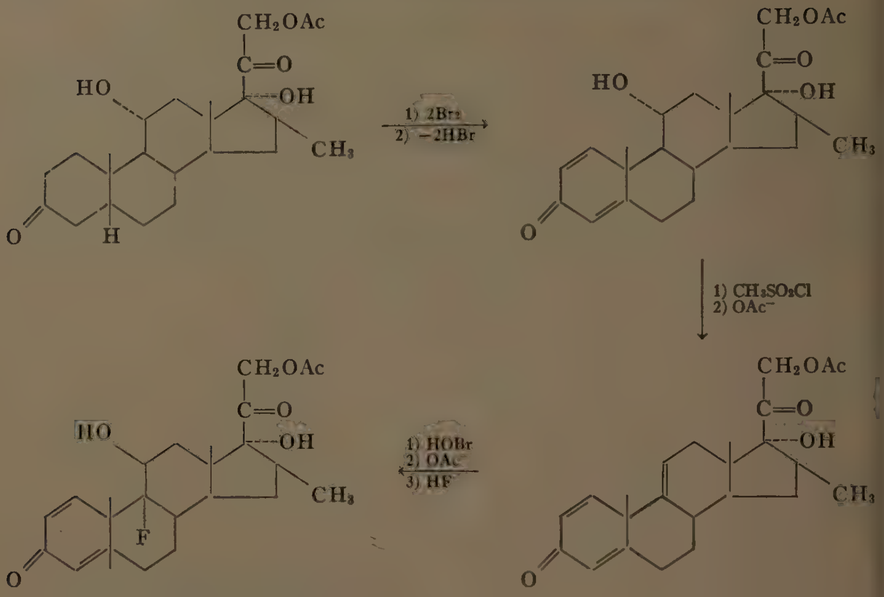


FIGURE 8.

Treatment with sodium acetate produces a 9β,11β-oxide which, on opening with HF, gives 9α-fluoro-16β-methylprednisolone acetate[11] (FIGURE 9).

To prepare the 16α-methyl corticoids, the same starting material, 3α-acetoxy-16-pregnene-11,20-dione, is used. Reaction with a methyl Grignard reagent introduces the 16α-methyl group, and the remainder of the cortical side chain and elaboration of the A-ring is produced in the usual fashion (FIGURES 10 and 11) to produce 16α-methylcortisone acetate or 16α-methylprednisone acetate. The former is converted to 16α-methylcortisol acetate by protection of the 3- and 20-ketones as semicarbazones, reduction of the 11-ketone to 11β-hydroxyl with sodium borohydride, and removal of the protective groups (FIGURE 12). The 11β-hydroxyl is dehydrated, and the 9α-fluoro-11β-hydroxyl group is introduced as before. Selenium dioxide treatment then gives 9α-fluoro-16α-methylprednisolone acetate[12] (FIGURE 13).

A much shorter route is that starting from diosgenin. This is converted to 16-dehydropregnenolone in only 3 steps and, by standard procedures, is trans-



9α-Fluoro-16β-methylprednisolone acetate

FIGURE 9.

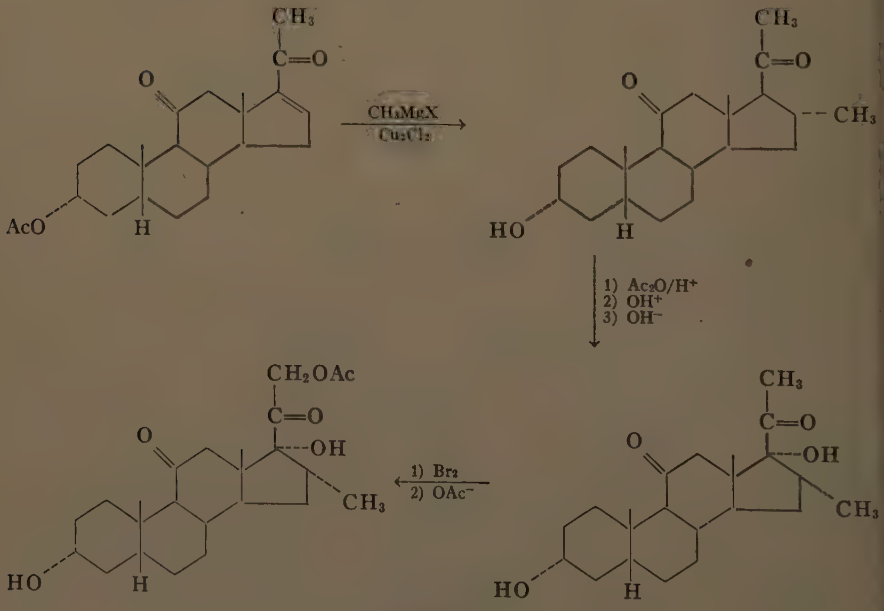


FIGURE 10.

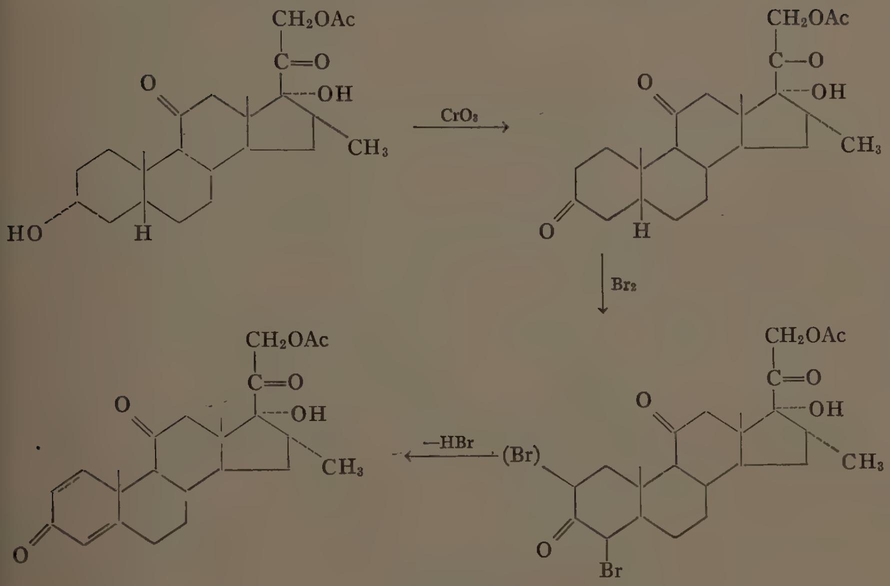
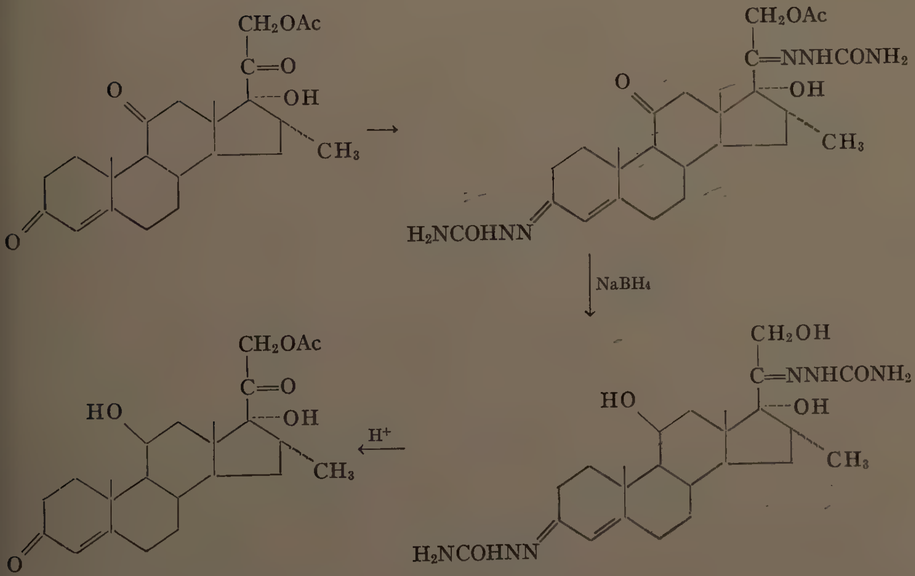


Figure 11.



16α-Methylcortisol acetate

Figure 12.

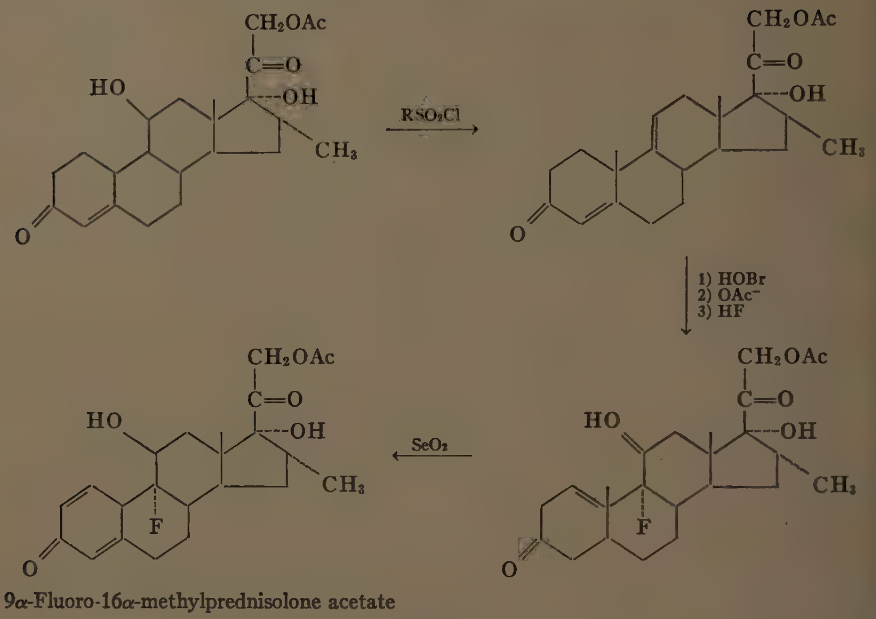


FIGURE 13.

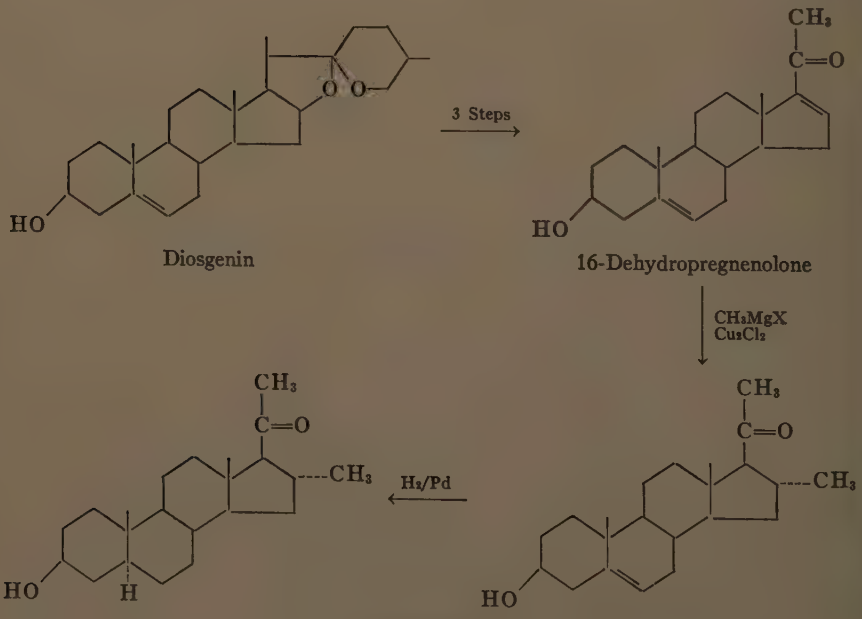


FIGURE 14.

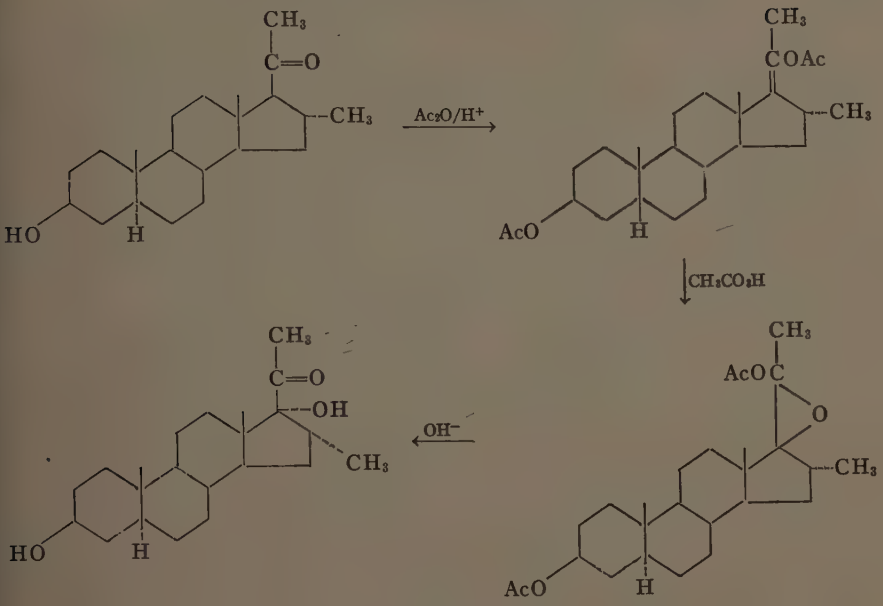


FIGURE 15.

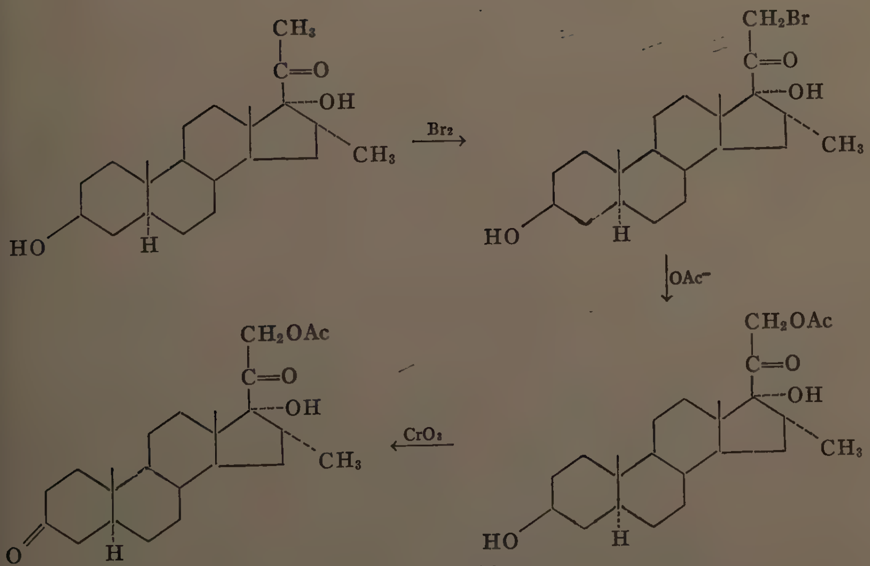
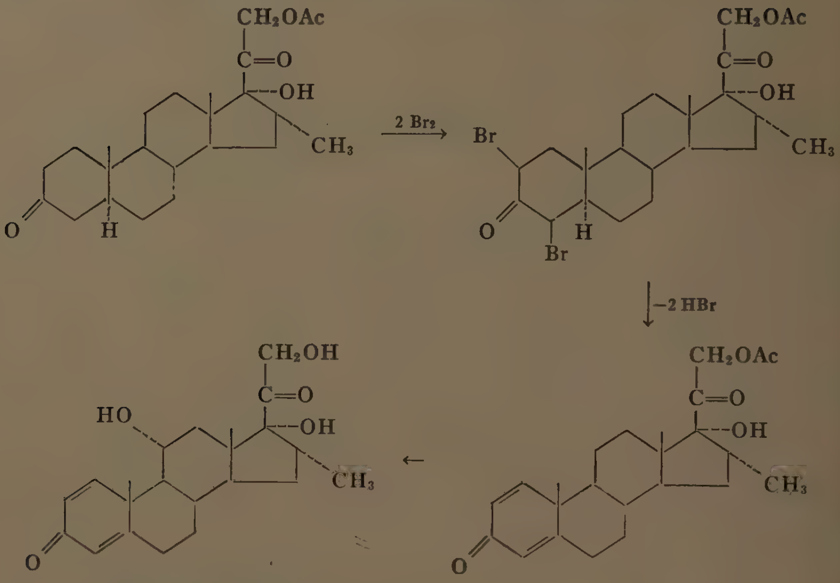


FIGURE 16.



16α-Methyl-1-dehydro-11-epicortisol

FIGURE 17.

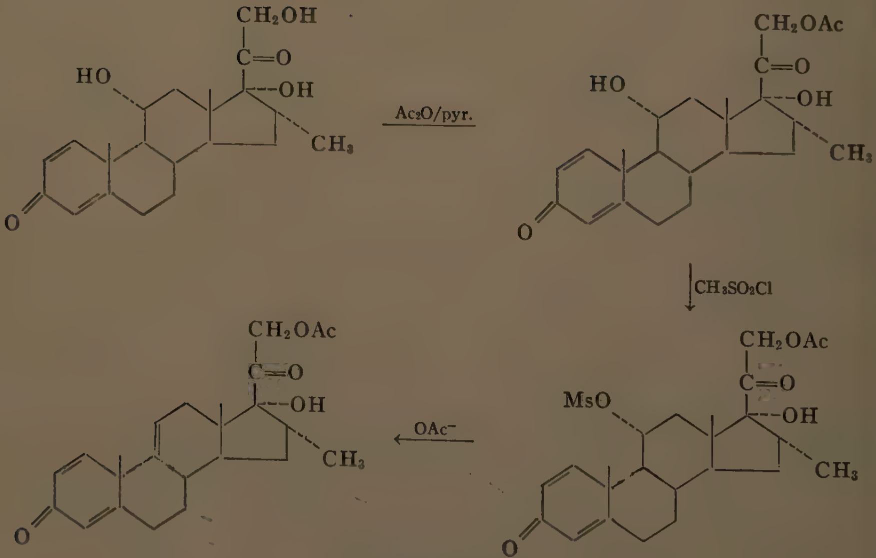
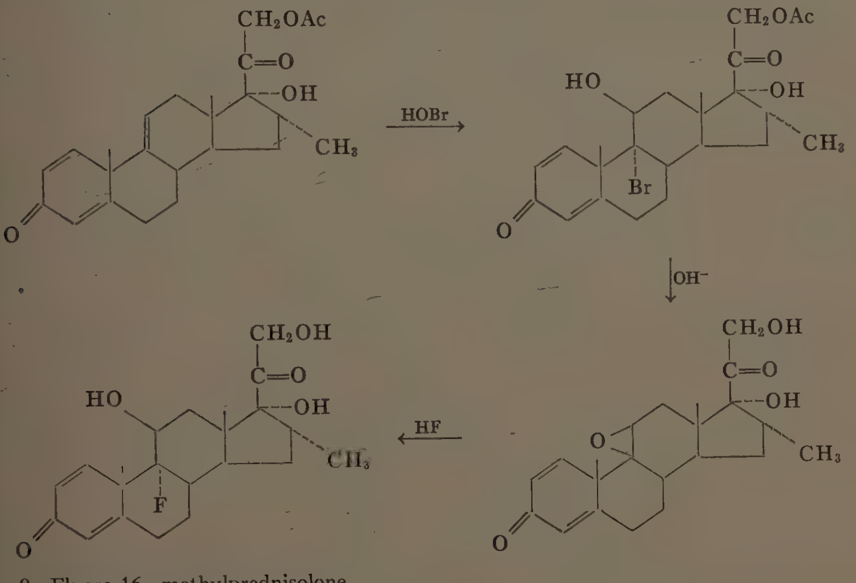


FIGURE 18.

formed to 16α-methyl-1-dehydro-Compound S 21-acetate, which is microbiologically hydroxylated at C-11 to 16α-methyl-1-dehydro-11-epicortisol (FIGURES 14 to 17). In the usual fashion this is then transformed to 9α-fluoro-16α-methylprednisolone[13] (dexamethasone) as shown in FIGURES 18 and 19.



9α-Fluoro-16α-methylprednisolone
(dexamethasone)

FIGURE 19.

Acknowledgment

The following researchers at the Schering Corporation were intimately connected with the 16-methyl corticoid program: F. Carlon, C. Coniglio, W. Gebert, H. Harris, E. B. Hershberg, H. Herzog, A. Mitchell, N. Murrill, A. Nussbaum, R. Rausser, and L. Weber.

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THE BIOLOGY OF ANTI-INFLAMMATORY STEROIDS

Robert H. Silber
Merck Institute for Therapeutic Research, Rahway, N. J.

This presentation will be restricted to essentially 3 topics: (1) the assay of 16-methyl corticosteroids as anti-inflammatory agents; (2) assay techniques employed in the Merck Institute for Therapeutic Research, Rahway, N. J., with some discussion of potential difficulties inherent in these assays; and (3) limited metabolic studies conducted with the most potent of the steroids tested—dexamethasone.

The results of granuloma inhibition and liver-glycogen assay of the 16α-methyl[1, 2] and 16β-methyl[3, 4, 5] steroids are shown in TABLE 1. The introduction of a 16-methyl has increased the potency in the granuloma test, in comparison with the values found with the related steroids in the same tests, as shown in the lower part of the table. The 16α-methyl has also increased the glycogen-deposition potencies. The 16β-methyl group, in contrast, either decreased the glycogenic potencies or left them essentially unchanged. In both series, however, the glycogen activities were disproportionately low, suggesting that these steroids might prove to have relatively less effect on insulin requirements.

The clinical potencies of the 16α-methyl steroids, taken from Boland,[6] are also shown in TABLE 1. It is apparent that the glycogenic potencies show a fairly close correlation with clinical efficacy; this, of course, could be fortuitous. In any case, both animal tests described below have revealed the correct order of activity for the 16α-methyl series. From the animal studies, it was anticipated that clinical experience would show dexamethasone to be at least as potent as 9α-fluoroprednisolone, but without the sodium-retaining property of the latter (described below), and possibly with relatively less effect on carbohydrate metabolism.

Clinical potencies of the 16β-methyl steroids remain to be established, but it should be recognized that, although potencies derived from animal data have been reasonably predictable, it seems likely that, as the structures of new steroids become progressively more complex, more discrepancies between animal and clinical data will appear.

The oral route of administration is employed in both animal tests to minimize differences in absorption. As shown previously,[7] there are striking differences in absorption of various steroids from subcutaneous injection sites (TABLE 2), and it was noted that such differences could complicate assay data seriously. To illustrate this point, the results of a study (carried out in collaboration with H. C. Stoerk) of the effect of route of administration on a granuloma assay are shown in TABLE 3. Hydrocortisone acetate theoretically should be 0.9 as potent as hydrocortisone, but after subcutaneous injection it was only 0.2 as active and, after intraperitoneal injection, it was 3 times as effective. In the oral test, no difference between the 2 forms was detected. Obviously, for a proper comparison of these or comparable steroids the oral route is preferred. As an added precaution, one can make comparisons between similar forms of

TABLE 1
POTENCIES OF 16-METHYL STEROIDS

Steroid	Glycogen × F	Granuloma × F	Clinical potency (Δ^1F × 4)*
16α-Methyl F	2	3	3
16α-Methyl-Δ^1F	5	16	5
16α-Methyl-9α-fluoro F	12	36	13
Dexamethasone	20	200	30
16β-Methyl F	0.6	4	
16β-Methyl-Δ^1F	1.5	23	
16β-Methyl-9α-fluoro F	8.5	23	
16β-Methyl-9α-fluoro-Δ^1F	11	70	
Prednisolone	3–4	3–4	
9α-Fluoro F	8	6	
9α-Fluoro Δ^1F	13	12	

* From Boland.[6]

TABLE 2
ABSORPTION OF STEROIDS FROM SUBCUTANEOUS INJECTION SITES IN RATS

Steroid	Injected mg./100 gm. body weight	Percentages absorbed in 1 week
Cortisone acetate	10	50.7
Cortisone	9	73.7
Hydrocortisone acetate	10	19.3
Hydrocortisone	9	98.0

TABLE 3
GRANULOMA INHIBITION
Comparison of Routes of Administration*

Steroid	Daily dose mg., route	Granuloma mg.	Potency × F
Hydrocortisone	1.5 S.C.	22 ± 1.3	—
	4.5 S.C.	18 ± 0.5	
Hydrocortisone acetate	1.5 S.C.	28 ± 2.2	0.2
	4.5 S.C.	24 ± 0.6	
Hydrocortisone	1.5 I.P.	29 ± 1.7	—
	4.5 I.P.	23 ± 0.7	
Hydrocortisone acetate	1.5 I.P.	23 ± 1.4	3.0
	4.5 I.P.	21 ± 0.6	
Hydrocortisone	1.5 P.O.	28 ± 2.3	—
	4.5 P.O.	22 ± 1.2	
Hydrocortisone acetate	1.5 P.O.	28 ± 1.7	1.0
	4.5 P.O.	21 ± 0.6	
Control	—	54 ± 1.5	

* Six rats per group.

steroids, such as 21-phosphates with hydrocortisone 21-phosphate, and 21-alcohols with hydrocortisone (*not* hydrocortisone acetate).

*Granuloma Inhibition**

The granuloma-inhibition test is conducted in intact male Holtzman rats fed Purina Lab Chow ad libitum. Two weighed, sterile, cotton pellets, cut from dental rolls, are inserted under the skin of the abdomen, and oral doses of 0.5 to 4.5 mg. of hydrocortisone (or equivalent amounts of other steroids) are administered daily for 1 week. One day after the last dose, thymus (wet) and granuloma (dry) weights are determined, and the effects of the test steroid are estimated in comparison with those of hydrocortisone. Adrenal and body-weight changes also occur, but do not appear to be as reproducible or as quantitative in this test; these effects are studied in other experiments to be described later. In TABLE 4, typical granuloma data are presented, with dexamethasone shown about 200 times as potent as hydrocortisone in both intact and adrenalectomized rats.

TABLE 4
GRANULOMA INHIBITION

	Daily dose mg.	Thymus mg.	Granuloma mg.
Intact rats, 119 gm., 5 per group			
Dexamethasone*	0.005	222 ± 6	41 ± 2
	0.015	78 ± 4	27 ± 1
	0.045	46 ± 7	20 ± 1
Hydrocortisone*	0.5	359 ± 27	43 ± 2
	1.5	268 ± 4	35 ± 2
	4.5	120 ± 19	23 ± 2
Control	—	505 ± 25	51 ± 4
Adrenalectomized rats, 166 gm., 6 per group			
Dexamethasone†	0.0025	444 ± 25	58 ± 2
	0.0075	189 ± 21	36 ± 2
	0.0225	58 ± 2	20 ± 1
Hydrocortisone†	0.5	535 ± 32	60 ± 2
	1.5	389 ± 41	38 ± 4
	4.5	160 ± 12	23 ± 1
Control	—	804 ± 52	64 ± 2

* Dexamethasone about 160 times as potent as hydrocortisone.
† Dexamethasone about 240 times as potent as hydrocortisone.

Liver-Glycogen Deposition†

In the liver-glycogen deposition test intact CFW mice are fasted overnight and a stock solution of steroid in absolute ethanol is prepared at concentrations of 2 or 4 mg./ml. A total of 10 to 100 μg. of hydrocortisone or the equivalent, in 2.5 ml. of 1 per cent ethanol, prepared from the stock solution, is administered by metal catheter in 5 equal hourly doses. One hour after the final dose, the entire liver is removed and total liver glycogen or reducing substances are determined. Values are calculated in terms of milligrams of glucose per 10 gm. of body weight. Typical data for both adrenalectomized and intact mice are shown, with standard errors, in TABLE 5. Dexamethasone was about 20 times as potent as hydrocortisone in these tests.

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* Based on R. Meier et al.[8]
† Based on Reinecke and Kendall.[9]

Sodium Excretion

None of the 16-methyl steroids in TABLE 1 caused sodium retention in the adrenalectomized rat in the procedure as performed by H. C. Stoerk of our laboratory. Adrenalectomized rats, on a low-sodium and low-potassium diet for 24 hours, are injected intraperitoneally with 5 ml. of saline and subcutaneously with 50 or 100 μg. of steroids in 0.25 ml. of 30 per cent ethanol. Untreated, prednisolone-treated, and desoxycorticosterone-treated rats are included in each experiment as controls. As shown in TABLE 6, dexamethasone does not cause sodium retention in this test. Excretion of sodium was essentially the same after administration of 100 μg. of hydrocortisone or dexamethasone.

TABLE 5
LIVER-GLYCOGEN DEPOSITION

	Total dose μg/mouse	Liver glycogen mg./10 gm. mouse
Intact mice, 6 per group		
Dexamethasone*	0.5	5.6 ± 0.59
	1.5	8.5 ± 1.57
	4.5	9.8 ± 1.03
Hydrocortisone*	10	6.0 ± 0.57
	30	8.1 ± 1.03
	90	10.0 ± 0.61
Control	—	4.9 ± 0.35
Adrenalectomized mice, 4 per group		
Dexamethasone*	0.5	4.2 ± 0.29
	1.5	5.5 ± 0.14
	4.5	5.9 ± 0.57
Hydrocortisone*	10	3.8 ± 0.09
	30	5.6 ± 0.30
	90	6.1 ± 1.12

* Dexamethasone about twenty times as potent as hydrocortisone in both tests.

Body-Weight Study in Rats

The body, thymus, and adrenal weights of rats have long been known to be depressed by corticosteroid treatment. If graded concentrations of hydrocortisone, prednisolone, or related steroids are fed in the diet, it is possible to compare the effects and to determine whether the anti-inflammatory potency (granuloma inhibition) can be disassociated from these catabolic or antianabolic manifestations of corticosteroid activity.

In TABLE 7, sample data show that these effects paralleled the potencies in the granuloma test for each of the steroids fed.

Metabolic Studies with Dexamethasone

The exceptional potency of dexamethasone theoretically could be a result of greater intrinsic activity or of an alteration in metabolism of the steroid. The plasma half life of prednisolone in beagle dogs[10] has been found to be 1 hour, whereas that of hydrocortisone was somewhat shorter: 45 min. Although it might be difficult to explain the increased activity of prednisolone by means of a 33 per cent increase in plasma half life, the increase indicated that a change in metabolism had resulted from the introduction of the Δ^1 double bond and, obviously, an increased half life is not inconsistent with greater activity. Urinary analyses showed that, in fact, there had been an effect on metabolism, in that reduction and conjugation of the A ring had been inhibited.

When dexamethasone was administered intravenously to two beagle dogs, the plasma half life was found to be approximately the same as that of prednisolone. Thus, no clue regarding the exceptional activity of this steroid was found.

TABLE 6

URINARY SODIUM TEST IN ADRENALECTOMIZED RATS*

Steroid	Injected µg.	Sodium mEq./3 rats/5 hr.
Desoxycorticosterone	100	0.3
Hydrocortisone	100	0.88
Prednisolone	100	1.1
Dexamethasone	100	0.84
Control	—	0.82

* Stoerk.

TABLE 7

BODY-WEIGHT STUDY IN RATS HAVING STEROIDS INCORPORATED IN THE DIET*

Steroid	mg./kg. Diet	Final body weight, gm.	Thymus mg.	Adrenals mg.	Potency × Δ^1F	Granuloma potency†
16α-Methyl F	75	166	84	19	0.5–0.6	0.75
16α-Methyl-Δ^1F	10	165	101	21	3–4.7	4
Dexamethasone	0.5	172	158	24	40–56	50
16β-Methyl F	25	178	167	23	0.8–1.0	1
16β-Methyl-Δ^1F	7.5	163	95	21	4.0–6.5	6
16β-Methyl MK-125	1.5	176	185	24	14–17	18
Prednisolone	10	186	290	29		
	30	171	137	21		
Control	—	203	544	38		

* One-week experiment, 5 rats per group, 169 gm. each.
† In terms of hydrocortisone divided by 4, included here for comparison.

However, just as introduction of the Δ^1 double bond stabilized the A ring in prednisolone, the introduction of 16α-methyl has been found to stabilize the side chain (TABLE 8). The steroids were incubated for 44 hours at 37° C. with 9 ml. of human plasma containing 1 mg. each of penicillin and streptomycin. An average of 35 per cent of the side chain was lost from the steroids without the 16α-methyl, whereas only 13 per cent was lost from the 4 steroids with this function. The phenylhydrazine-sulfuric acid procedure[11] was employed for this measurement. The side chain apparently is either split off or reduced on incubation so that it is no longer detected by the chemical test. Incidentally, the shapes of the curves obtained by reading the samples at 380, 410, and 440 mμ indicated that the steroid that remained had not been reduced in the A ring.

TABLE 8

STABILITY OF SIDE CHAIN IN HUMAN PLASMA*

Steroid	Percentage loss on incubation
16α-Methyl F	16
16α-Methyl-Δ^1F	8
16α-Methyl-9α-fluoro F	8.5
Dexamethasone	18.5
F	34
Δ^1F	44.5
9α-Fluoro F	30.5
9α-Fluoro-Δ^1F	32.5

* Forty-four hours at 37° C.; 20 μg. in 9 ml. plasma.

TABLE 9

BINDING IN HUMAN PLASMA*

Steroid	Percentage bound
16α-Methyl F	73.5
16α-Methyl-Δ^1F	79
16α-Methyl-9α-fluoro F	73
Dexamethasone	61.5
F	79
Δ^1F	73.5
9α-Fluoro F	74
9α-Fluoro-Δ^1F	60

* Four days at 5° C.; 40 μg. in 8 ml. plasma.

A study of binding in human plasma was also carried out (TABLE 9). Forty μg. of steroid in 2 ml. of saline was mixed with 8 ml. of human plasma and dialyzed against 10 ml. of saline at 5° C. for 4 days. Identical samples were prepared and kept frozen until the end of the experiment to serve as standards, and a similar set of samples, both for dialysis and for standards, was prepared in saline to serve as controls. Analyses of the dialyzed plasma and the dialyzate showed that dexamethasone was bound to about the same degree as 9α-fluoroprednisolone, and both were bound less than the other steroids studied.

The urinary excretion of 17,21-dihydroxy-20-ketosteroids in free and conjugated form, after both oral and intravenous administration to dogs, gave results comparable to those obtained after administering prednisolone.[8] After oral administration of 50 mg., 3.12 mg. was found in the free form in the 24-hour urine, and an additional 1.6 mg. was detected after glucuronidase treatment (conjugated form). After intravenous administration of 25 mg., 1.25 mg. of free and 0.85 mg. of conjugated steroid were found.

In summary the 16α- and 16β-methyl steroids were more potent in the granuloma-inhibition test than their nonmethylated counterparts. The 16α-methyl forms were also more active in the liver-glycogen deposition test, whereas introduction of the 16β-methyl left the glycogenic potency either unchanged or reduced. The relatively lower glycogenic potencies of these steroids suggested that they might affect insulin requirements less than anticipated.

The clinical potencies of the 16α-methyl steroids paralleled fairly closely their glycogen-deposition potencies, but this could be fortuitous. Both tests revealed the correct order of activity.

The introduction of a 16-methyl reduced the severe sodium-retention properties of the 9α-fluoro corticosteroids.

Potential assay hazards due to absorption differences have been re-emphasized.

Body-, adrenal-, and thymus-weight depression of several of these steroids have been shown to parallel the potency in the granuloma test.

Although dexamethasone was more stable and was bound to a lesser degree in human plasma, its plasma half life and urinary excretion were not significantly different from those of prednisolone.

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LABORATORY EVALUATION OF ANTI-INFLAMMATORY STEROIDS

Sibylle Tolksdorf
Schering Corporation, Bloomfield, N. J.

Our objectives in testing cortical steroids are, first, to establish the type of biological activity, namely glucocorticoid, anti-inflammatory, or mineralocorticoid; second, to obtain a quantitative estimation of potency; third, to study the correlation between structure and activity; and, fourth, to predict the clinical usefulness of a new steroid. The predictive value of several classic glucocorticoid methods is illustrated in TABLE 1. The reported potency ratios for six naturally occurring active compounds show excellent agreement between the different assays on the one hand and between glucocorticoid and clinical activity on the other hand. Among synthetic steroids, only prednisone and prednisolone maintain perfect correlation between all test parameters and therapeutic activity. Methylprednisolone has a somewhat high potency by the liver-glycogen method, and the liver-glycogen responses of 9α-fluoroprednisolone and triamcinolone have no relation whatever to the clinical efficacy of these steroids. The thymus involution assay also gives potency ratios that are too high. This finding seriously compromises the predictive value of these two classic test methods. The eosinophil assay, on the other hand, shows excellent correlation with the therapeutic activity, and therefore appears to be a reliable measure of corticoid activity.

Methods

Prediction of the clinical usefulness of a new steroid obviously requires a broad spectrum of tests in order to ensure against false positive results. Some of the parameters currently investigated in our laboratory are shown in TABLE 2.

The 4-hour eosinophil assay is carried out in epinephrine-treated, adrenalectomized, C_{57} brown mice.[5, 19, 20] For statistical analysis, the log ratio of the P.M. count plus 1 divided by the A.M. count is used as the criterion of response. The average precision of 12 assays was $\lambda = 0.22$. A standard 4-point assay using 20 mice is expected to estimate the potency with an average standard error of ±22 per cent. Approximately 6 per cent of the assays require repetition because of inordinately large values of λ. The test is based on a physiological response that occurs in other species, including the human subject.

In contrast to the eosinophil assay, all tests of anti-inflammatory properties that lend themselves to quantitation in terms of dose-response curves are highly artificial. A modification of the Selye croton-oil granuloma-pouch test,[21] patterned after Robert and Nezamis,[22] is used in our laboratory. The steroid is applied locally, by subcutaneous injection, 24 hours before the preparation of the pneumoderma. The volume of exudate obtained at autopsy 6 days later is used as the criterion of response. Cortisone acetate, hydrocortisone acetate, prednisone, prednisolone, and their acetates are used as standards. Some typical standard curves are shown in FIGURE 1. Statistical analysis of a series of standards shows no significant differences between the slopes of these steroids and a very high degree of precision, with an average value of $\lambda = 0.10$. Hence, a standard 6-point assay employing 30 rats provides a potency estimate with a relative standard error of ±8 per cent.

The biological significance of the granuloma-pouch assay has been of interest to us. The test appears to correlate with the reported intra-articular effects of corticosteroids in the clinic. It will be recalled that cortisone acetate is inactive in the patient by this route of administration, whereas hydrocortisone acetate and prednisolone acetate are highly effective. In the pouch, prednisone acetate has one fifth the activity of prednisolone acetate, and cortisone acetate one quarter the activity of hydrocortisone acetate. On the other hand, prednisolone alcohol is 0.9 times as active as prednisone alcohol. Another characteristic feature of the granuloma-pouch response is the enhanced activity of 21-acetates. Robert and Nezamis[22] found hydrocortisone acetate 5 times more active than the alcohol. It will be appreciated that it is imperative to assay 11-keto steroids, 11-hydroxy steroids, 21-alcohols, and 21-acetates against the appropriate standards in order to obtain meaningful results.

TABLE 1

BIOLOGICAL ACTIVITY OF SEVERAL NATURAL AND SYNTHETIC ADRENOCORTICAL STEROIDS

	Liver glycogen[1, 2]	Muscle work[3]	Thymus involution[4]	Eosinopenia[5, 6]	Therapeutic (rheumatoid arthritis)
Natural steroids					
Cortisone	1	1	1	1	1
Hydrocortisone	1.55	1.6	1.5–2.4	0.8–1	1–1.5
Corticosterone	0.54	0.46	0.2	0.37	0
11-Dehydrocorticosterone	0.48	0.32	0.2	0.24	0
11-Desoxycorticosterone	0.0–0.2	0.02	0	0	0
Aldosterone	0.33			0.25–0.5	0
Synthetic steroids					
Hydrocortisone	1		1	1	1
Prednisolone[7–10]	3.95		3.18	3.3	3
6-Methylprednisolone[11, 12, 27]	10			1.7[27]	3.4
9α-Fluoroprednisolone[8, 13–16]	25–49		13	7.2	6–9
Triamcinolone[17, 18, 27]	15–36		7	3.2[27]	3–4

TABLE 2

METHODS FOR EVALUATION OF CORTICOIDS

Method	Animal species	Dose range	Precision
Eosinopenia	ADX* mice	0.1–40 μg.	$\lambda = 0.22$
Croton oil granuloma	Intact rats	0.05–5 mg.	$\lambda = 0.10$
Water, Na, K excretion	ADX rats	0.1–800 μg.	
Thymus involution	Weanling rats	0.2–1.6 mg.	$\lambda = 0.40$
Eosinopenia	ADX dogs	2.5 mg.	
Balance studies: N, water, Na, K, Ca	Trained dogs		

* Adrenalectomized.

The electrolyte excretion is measured in adrenalectomized rats during a 6-hour period by a modification of the method of Cook and Elmadjian.[23] This also is a somewhat artificial test, but it is adequate to distinguish between diuretic and sodium-retaining steroids. The thymus-involution assay is used as a confirmatory bioassay for glucocorticoid activity. It is carried out in weanling rats according to Stephenson.[4]

The adrenalectomized dog affords a welcome confirmation of eosinopenic activity in another species.[24] Other parameters, such as duration of activity and the effects of different routes of administration, are readily studied in this preparation. For metabolic studies, intact beagle dogs are maintained on a synthetic diet[25] supplemented with vitamins. The metabolic studies in the dogs[26] are patterned after those performed in human subjects and appear to give information closely related to that found for man.

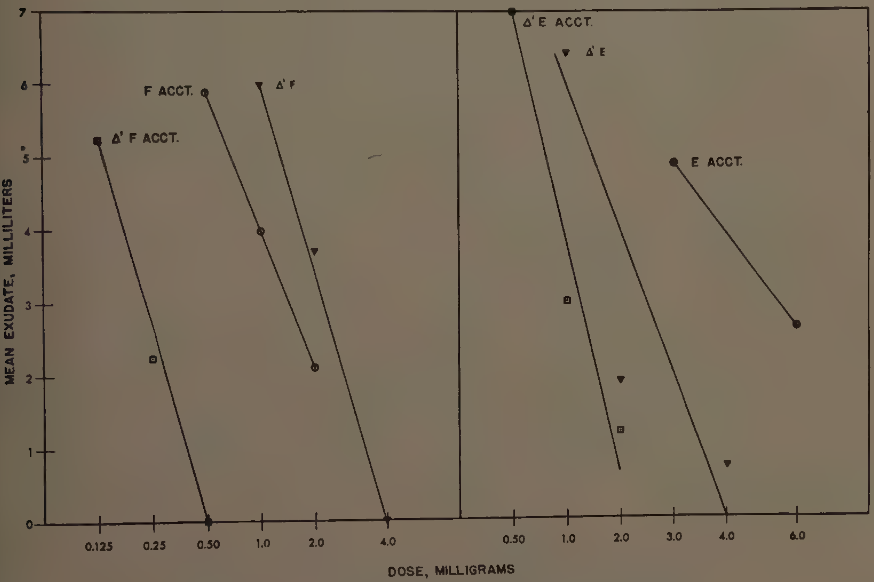

FIGURE 1. Typical standard curves of pouch assays.

Effect of C_{16}-Methylation on Biological Activity

The effects of 16α- and 16β-methylation on 11-desoxy steroids, on 11-keto-steroids, and on 9α-fluoro-11-hydroxy steroids have been investigated. In the cortisone and prednisone series (TABLE 3), eosinopenic activity remained unchanged within the limits of the assay. Anti-inflammatory activity appeared slightly increased by 16β-methylation and slightly depressed by 16α-methylation. Opposite effects were observed in the case of 9α-fluoroprednisolone (TABLE 4), where 16α-methylation increased anti-inflammatory activity by a factor of 1.23 and eosinopenic activity by a factor of 1.29, while 16β-methylation depressed the anti-inflammatory activity of the parent steroid by half. The activity of 9α-fluoroprednisolone in the granuloma-pouch test was approximately 4 times that of prednisolone, and dexamethasone had 5 times the anti-inflammatory activity of prednisolone. The same anti-inflammatory potency ratios were obtained with the 21-acetates of prednisolone, dexamethasone, and the 16β-methyl analogue.

The thymus-involution assay, on the other hand, gave dexamethasone and its acetate an apparent potency 25 times greater than that of prednisolone and prednisolone acetate. The 16β-methyl analogue was 4 times more active than the standard.

TABLE 3
EFFECT OF 16-METHYLATION ON CORTICOID ACTIVITY

Steroid*	Anti-inflammatory activity†	Eosinopenic activity
E acetate	1	1
16β-Me-E acetate	2.1 (1.6–2.8)	0.65 (0.37–1.72)
Δ^1E acetate	1	1
16α-Me-Δ^1E acetate	0.64 (0.53–0.69)	0.86 (0.42–1.98)
16β-Me-Δ^1E acetate	1.35 (1.18–1.58)	0.71 (0.46–1.04)
Δ^1E	1	1
16β-Me-Δ^1E	1.35 (0.93–2.09)	0.88 (0.24–2.61)

* E represents cortisone; Δ^1E, prednisone.

† Figures in brackets are 95 per cent fiducial limits.

TABLE 4
EFFECT OF 16-METHYLATION ON CORTICOID ACTIVITY OF 9α-FLUOROPREDNISOLONE

Steroid*	Anti-inflammatory activity†	Eosinopenic activity	Thymus involution‡
Δ^1F	1	1	1
9-Fluoro-Δ^1F	4.34 (3.81–4.95)	2.4 (1.4–4.5)	
16α-Me-9α-fluoro-Δ^1F	5.08 (4.67–5.51)	3.1 (1.7–6.8)	25.8
16β-Me-9α-fluoro-Δ^1F	2.42 (2.07–2.82)	5.1 (3.6–7.7)	
Δ^1F acetate	1	1	1
16α-Me-9α-fluoro-Δ^1F acetate	4.93 (4.10–5.93)	5.8 (2.94–11.1)	25 (10–32)
16β-Me-9α-fluoro-Δ^1F acetate	2.47 (1.96–3.12)	2.3 (1.66–3.24)	4.35 (3.54–5.36)

* Δ^1F represents prednisolone; 16α-Me-9α-fluoro-Δ^1F, dexamethasone.

† Figures in brackets are 95 per cent fiducial limits.

‡ A comparative thymus involution assay showed dexamethasone to be 1.03 times as active as dexamethasone acetate; 95 per cent fiducial limits were 0.80–1.34; $\lambda = 0.24$.

The effect of 16-methylation on the mineralocorticoid pattern was very striking (TABLE 5). The sodium retention of 1,4-pregnadiene-17α, 21-diol-3,20-dione (Δ^1S) is converted into sodium excretion. The diuretic property of prednisone acetate is greatly enhanced and the sodium retention of 9α-fluoroprednisolone acetate is completely abolished by the introduction of the 16-methyl group. An attempt was made to produce comparable diuretic effects with prednisolone and dexamethasone in order to assess quantitatively the increase in diuresis (TABLE 6). It seems safe to say that in the rat dexamethasone is roughly 10 times as diuretic as prednisolone and prednisone.

TABLE 5

EFFECT OF 16-METHYLATION ON WATER AND ELECTROLYTE EXCRETION*

Dose µg.	No. of rats	Water	Na	K	No. of rats	Water	Na	K	No. of rats	Water	Na	K
	Δ^1S				16α-Me-Δ^1S				16β-Me-Δ^1S			
800	9	111	71	105	10	175	152	376	5	148	128	154
200	9	90	68	109	10	149	170	274	9	125	122	145
50	5	104	62	78	15	140	150	202	8	107	121	97
12.5					10	90	88	117	5	76	93	110
3.125					10	79	85	125	5	89	70	128
	Δ^1E acetate				16α-Me-Δ^1E acetate				16B-Me-Δ^1E acetate			
800	4	211	108	194	5	230	199	214	4	270	111	295
200	5	177	111	165	10	184	159	201	3	267	155	215
50	5	152	79	125	10	179	191	170	5	211	145	255
	9α-fluoro-Δ^1F acetate				16α-Me-9α-fluoro-Δ^1F acetate				16β-Me-9α-fluoro-Δ^1F acetate			
50	5	220	46	734†	5	303	111	707†	5	236	111	945†
10	5	224	67	597	5	324	131	582	5	233	133	880
2	5	148	44	312	5	228	130	327	5	170	132	405
0.5	5	103	56	177	5	138	93	183	5	111	123	105

* Excretion is expressed in percentages of that of the respective control groups, with controls equal to 100. Δ^1S is 1,4-pregnadiene-17α,21-diol-3,20-dione; Δ^1E, prednisone; Δ^1F, prednisolone; 16α-Me-9α-fluoro-Δ^1F acetate, dexamethasone acetate.

† The potassium excretion of the control groups in this series of experiments was considerably lower and the sodium-potassium ratio considerably higher than the year's average values.

TABLE 6

MINERALOCORTICOID ACTIVITY OF PREDNISOLONE AND DEXAMETHASONE*

Dose µg.	No. of rats	Water	Na	K	Dose µg.	No. of rats	Water	Na	K
	Prednisolone					Dexamethasone			
30	5	182	113	235	0.9	5	204	142	261
10	5	146	120	175	0.3	10	116	91	124
3.3	5	139	107	110	0.1	10	96	75	92
					0.03	5	111	80	83
	Prednisolone acetate					Dexamethasone acetate			
30	5	181	158	227	0.9	5	159	133	211
10	5	185	174	196	0.3	9	122	101	143
3.3	4	144	126	150	0.1	9	105	86	102
					0.03	5	111	72	85

* Excretion is expressed in percentages of that of the respective control groups, with controls equal to 100.

In the adrenalectomized dogs, 1 mg. of dexamethasone orally produces maximal eosinopenia in 6 hours; the same effect is obtained with 5 mg. of prednisone. No difference was noted between the alcohol and acetate of dexamethasone (FIGURE 2).

Metabolic studies with dexamethasone acetate indicate that this steroid produces the typical effects of glucocorticoids, such as negative nitrogen and calcium balance, as well as polydypsia and polyuria, which is a characteristic response of the dog to glucocorticoids.[26]

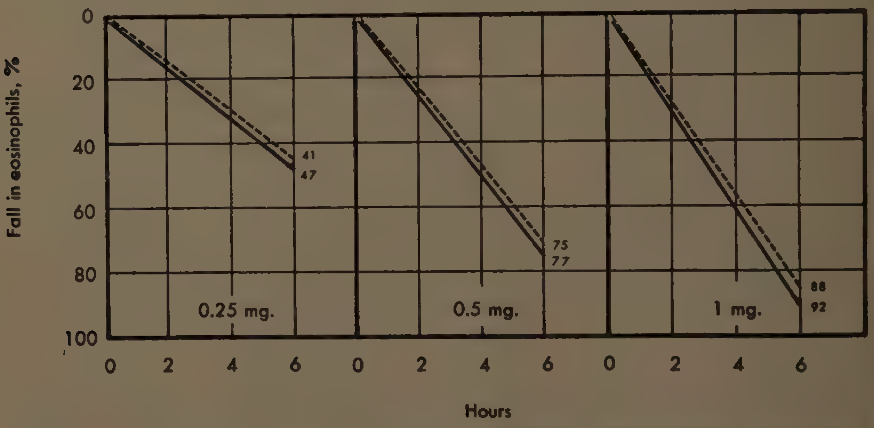

FIGURE 2. Eosinopenic activity of orally administered dexamethasone in adrenalectomized dogs. *Dashed line* represents alcohol; *solid line*, acetate.

Summary

We have discussed some of the laboratory methods that, in our hands, are useful guides for the evaluation of synthetic steroids.

The effects of 16α- and 16β-methylation on anti-inflammatory, eosinopenic, and mineralocorticoid activity of cortical steroids have been investigated.

Dexamethasone has 5 times the anti-inflammatory and eosinopenic activity of prednisone and prednisolone, and is 10 times more diuretic than these steroids.

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Discussion of the Paper

Question: As clinicians, we know that the steroids presently on the market all result in some trouble for the clinicians. We noted in early days that they produced sodium retention, for example. Through the efforts of the chemists, this side effect has now been diminished, but one side effect, superimposed infection, still remains unsolved. Are there laboratory methods for early detection of this side effect, for the guidance of the steroid therapist?

Sibylle Tolksdorf: I am afraid we have no methods to guard against that side effect of steroids and, from my limited knowledge of the clinical literature, it is my impression that it has been greatly overrated. As an example, in the treatment of leukemia, corticoids are given at high doses for long periods, yet the incidence of infections, I think, is very small.

Part II. Metabolic Studies

ENZYMATIC METABOLISM OF CORTICOSTEROIDS

Gordon M. Tomkins
National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md.

The adrenal steroids can act as substrates for enzymatic reactions in the same way that other, more conventional biochemical reagents do. There are, however, several singularities about steroid substrates that are worthy of consideration. First, the rate of their production and their level in body fluids are considerably below those of many other biologically important compounds and, as a result, the activity of enzymes available for steroid hormone metabolism need be less than the activities of enzymes involved with more quantitatively significant systems such as glycolysis. By the same token, the steroid enzymes must be able to function efficiently at low substrate concentrations; that is, they must have a high affinity for their substrates. In addition, since the steroids are hormonally or pharmacologically active, any metabolic reaction they undergo may have a "double meaning"; not only as an interesting chemical process, but also as one with potential physiological consequences. An interesting example of this is Talalay's recent demonstration[1] that the reversible oxidation of steroid alcohols can act as a mechanism for transferring hydrogen between the two large classes of pyridine nucleotides, diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN).

FIGURE 1 illustrates the reactive groups in cortisol that are subject to enzymatic attack in mammals. In general, the enzymes responsible for these metabolic conversions are not well characterized. Nevertheless, the transformations indicated have been observed both in *in vivo* and *in vitro*,[2] and there are undoubtedly enzymes available for carrying out the individual steps: reduction of the carbonyl group at 20 to both isomeric 20-alcohols;[3] oxidation-reduction at the 11-position,[4] resulting in the interconversion of a ketone and alcohol; hydroxylation of both the 2-[5, 6] and the 6-positions;[7] and, finally, reduction of the double bond at 4, with consequent loss in physiological activity. The present discussion will be concerned with the latter reduction, since it appears to be the rate-limiting step in the biological inactivation of the corticosteroids[8] and has been studied somewhat more extensively than the other reactions mentioned.[9, 10]

Upon the addition of 2 hydrogens to the 4–5 double bond, an asymmetric center at carbon 5 is produced, as shown in FIGURE 2. A 2-dimensional representation of the 2 possible isomers, the 5α- and 5β-pregnane compounds, does not do justice to the important configurational difference between these molecules. The A-B ring junction of the 5β isomer is buckled whereas, in the 5α isomer, the A and B rings occupy nearly the same plane (FIGURE 3). This structural difference may have physiological significance since, at least in the case of the male hormones, the 5β-reduced isomers are physiologically inert, while the 5α steroids are fully as active as the 4-unsaturated parent compound.[11]

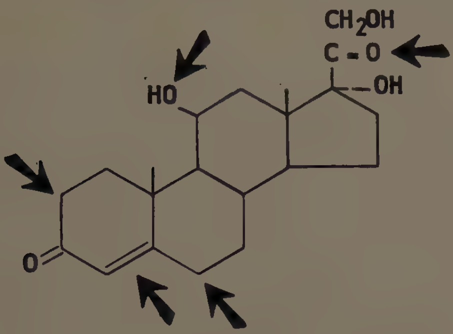


FIGURE 1. Points of attack (*arrows*) on cortisol.

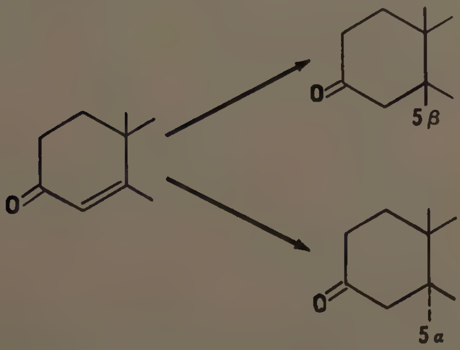
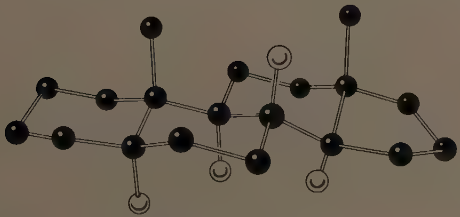


FIGURE 2. Isomers formed on reduction.



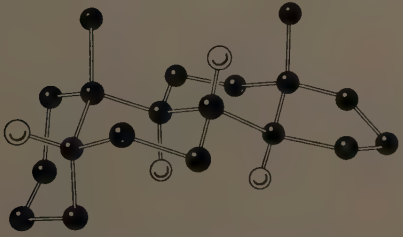


FIGURE 3.

It should be added, however, that the ring A-saturated corticoids appear to be biologically inactive.[12]

Biochemical Considerations

Δ^4 *Steroid reductases 5β.* The cytoplasm of mammalian liver contains a series of closely related enzymes, each of which catalyzes the reduction of the 4–5 double bond of a given α,β-unsaturated steroid to produce the 5β isomer.[9, 10]

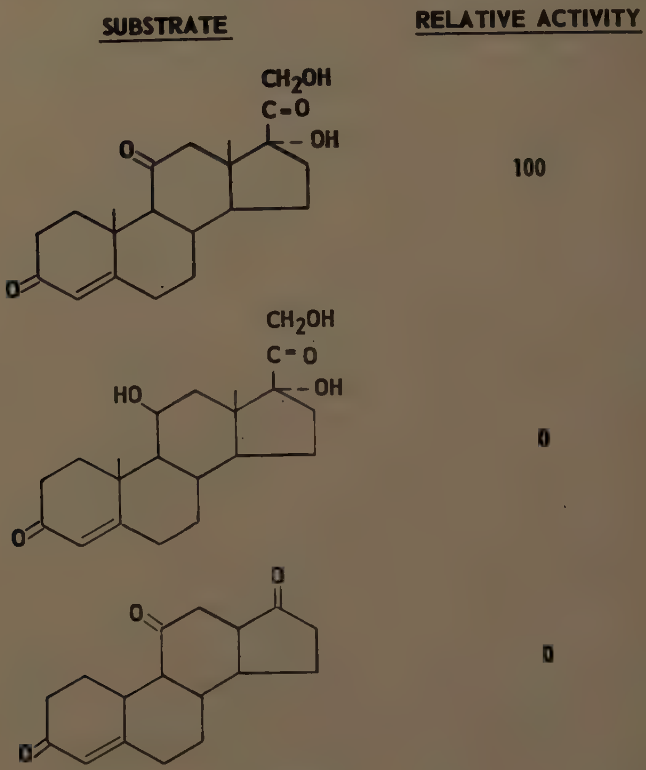


FIGURE 4.

The enzymes differ only with respect to their substrate specificity and, in this regard, are quite remarkable. In particular, an enzyme can be prepared from rat liver that catalyzes the reduction of the nuclear double bond of cortisone, but cannot react with cortisol, 17-hydroxy-11-deoxycorticosterone, or adrenosterone (FIGURE 4), indicating the exquisite sensitivity of the enzyme to the nature of the substituent at both the 11- and 17-positions. It is important to note that in crude extracts of rat liver there are enzymes that are active with respect to the reduction of all the substrates: cortisol, cortisone, adrenosterone, and 17-hydroxycorticosterone. Such striking specificity suggests biological overtones, although its actual significance is not clear at present.

It is interesting that rat liver also contains a soluble (cytoplasmic) enzyme for the reduction of the 1-unsaturation of Δ^1 cortisone,[9] and that this enzyme is not catalytically active toward Δ^1 cortisol; this indicates the same high degree of specificity as do the Δ^4 reductases.

It might be argued[13] that such specificity is an intrinsic part of steroid-protein interaction since, in order to achieve an effective enzyme-substrate union, short-range dispersion forces are involved that would result in a "tight fit" of the enzyme around the substrate. The relatively general substrate requirements of the 3α hydroxysteroid dehydrogenase of liver,[14] which can function with a variety of C_{19} and C_{21} steroids, makes the specificity of the double-bond reductases more exceptional, however.

An important feature of the reduction to the 5β isomer is that reduced TPN (TPNH) is the required hydrogen donor; reduced DPN (DPNH) is either totally inactive or considerably less active than TPNH (TABLE 1).

TABLE 1

PYRIDINE NUCLEOTIDE REQUIREMENT FOR STEROID REDUCTASE 5β*

Substrate	ΔOD_{240}/15 min.	
	TPNH	DPNH
Cortisone	210	0
Cortisol	115	0
17-Hydroxycorticosterone	120	0
Desoxycorticosterone	73	0

* All the reaction mixtures contained enzyme (0.50 to 0.70 saturated ammonium sulfate fraction) and substrate (100 μg. in 10 per cent methanol). For the TPNH experiment the following additions were made: TPN, 1.62 μmoles; isocitrate, 24 μmoles; $MgCl_2$, 4.6 μmoles; tris(hydroxymethyl)aminomethane (pH 7.4), 10 μmoles; and pig heart isocitric dehydrogenase in a total volume of 1.7 ml. For the DPNH experiments, in addition to enzyme and substrate, the following additions were made: DPN, 1.67 μmoles; ethanol, 2.2 mmoles; tris-(hydroxymethyl)aminomethane (pH 7.4), 10 μmoles; and crystalline yeast alcohol dehydrogenase in a total volume of 1.4 ml. Incubation was for 15 min. at 37° C. Activity was measured by decrease in optical density of substrate at 240 mμ as described in Tomkins.[10]

The 4-reductase reaction is irreversible, and attempts to introduce a double bond into ring A–saturated steroids by reaction (in the presence of the enzyme) with TPN have failed, even with a system that could reoxidize any TPNH that might have been formed: for example, TPN-cytochrome C reductase, cytochrome C, and cytochrome oxidase. The over-all reaction would be (with cortisone as substrate):

$$\text{dihydrocortisone} + \tfrac{1}{2}\, O_2 \rightleftharpoons \text{cortisone} + H_2O$$

One might infer, therefore, that the oxidation-reduction potential of the cortisone-dihydrocortisone couple is exceptionally high; indeed, several other pyridine nucleotide–linked reactions proceed almost exclusively in the direction of reduction.[15, 16] In the case of steroid reduction, however, it is apparent that the irreversibility of this reaction is not actually thermodynamic, but "biological," since Levy and Talalay[17] have found enzymes in a pseudomonad that can introduce double bonds into the A ring of a steroid nucleus in the presence of suitable electron acceptors:

$$\text{dihydrosteroid} + \text{dye} \rightleftharpoons \text{unsaturated steroid} + \text{dye-}H_2$$

This reaction also is irreversible. Since both saturation and unsaturation can be demonstrated, the potential is not such as to prevent the reaction from going in either direction, and specific enzymatic factors must be involved in the irreversibility of the reduction catalyzed by the liver enzymes, as well as in the irreversibility of the microbial oxidation. This seems paradoxical in view of the thermodynamically-based conclusion that enzymes do not influence the equilibrium of reactions that they catalyze, although a similar case is that of the transhydrogenase of *Pseudomonas fluorescens* described by Kaplan and his group.[18] Here, hydrogen transfer from TPNH to DPN proceeds without difficulty, but the reverse reaction will not occur except in the presence of 2′-adenylic acid, despite the fact that the oxidation-reduction potentials of both the DPN and TPN couples are identical.

Δ^4 *Steroid reductases 5α.* The reduction of the 4 double bond to the 5α steroid is catalyzed, of course, by a different system from the 5β reaction since, as seems universally true, enzymatic reactions are stereospecific. This reduction has been studied by Forchielli and Dorfman[7] and has been reported to be catalyzed by a single microsomal enzyme. We have examined this system and have found that many of its characteristics are similar to those of the soluble 5β enzymes. Both are restricted largely to the liver. Activity has not been detected in other tissues, including various endocrine tissues such as testis or adrenal, although it has been reported that the eviscerated rat[19] and fibroblasts in tissue culture[20] reduce the double bond.

TABLE 2

EFFECT OF THYROXINE ADMINISTRATION ON STEROID REDUCTASE 5α ACTIVITY*

Substrate	Relative activity		
	Control	Tx_1	Tx_2
Cortisone	1	1	1
Cortisol	0.77	0.87	0.6
17-Hydroxycorticosterone	1.2	1.9	1
11-Desoxycorticosterone	1.7	2.2	1.4
4-Androstene-3,17-dione	1.2	2.1	1.3

* The enzyme used was the microsomal fraction of rat liver from male animals. The controls were uninjected. Tx_1 and Tx_2 were injected with 0.5 μmole thyroxine per day for 20 days. The assay was carried out for 5 min. at 37° C. in the presence of a TPNH-generating system as described in TABLE 1.

Recent experiments[21] have suggested that the reductions of such closely related steroids as cortisone, cortisol, Compound S, deoxycorticosterone, and 4-androstene-3,17-dione are catalyzed by individual enzymes and not by a single protein that responds to any α,β-unsaturated steroid. Several types of experiments have been required to establish this point, since the enzymes have not been solubilized and therefore cannot be separated by conventional techniques. Perhaps the most dramatic illustration of this is the variation of the relative activities of these particulate 5α-steroid reductases when thyroxine is used as an enzyme inducer. When male rats were rendered thyrotoxic by the administration of thyroxine, the levels of all the 5α reductases increased,[22] but the ratios of their activitives varied a good deal in the course of their induction (TABLE 2), which is, of course, an indication that they are separate enzymes. Other experiments (TABLE 3) on rates of inactivation of the different activities give further support to this view.

A further similarity between the 2 systems is that the 5α reduction is also irreversible; this, again, is probably not a result of the free energies of the substrates and products, but of some factor introduced by each enzyme.

TABLE 3

STEROID REDUCTASE 5α INACTIVATION*

Substrate	Relative activity	
	0	6 hours
Cortisone	1.0	1.0
Cortisol	0.71	1.2
17-Hydroxycorticosterone	1.8	2.4
Desoxycorticosterone	1.9	3.2
4-Androstene-3,17-dione	2.2	3.1

* The enzyme used was the lyophilized microsomal fraction of female rat liver assayed immediately after resuspending in water (zero time) and 6 hours later. Assay is as described in TABLES 1 and 2. The absolute activity of the enzymes decreased about 50 per cent in 6 hours.

TABLE 4

PYRIDINE NUCLEOTIDE REQUIREMENT FOR STEROID REDUCTION 5α*

Substrate	ΔOD_{240}/5 min.	
	TPNH	DPNH
Cortisone	0.230	0
Cortisol	0.150	0
17-Hydroxycorticosterone	0.293	0
Desoxycorticosterone	0.405	0
4-Androstene-3,17-dione	0.395	0

* These reactions were run with microsomes from female rats for 5 min. at 37° C. TPNH and DPNH were generated as described in TABLE 1, and the reaction was assayed as described in TABLES 1 and 2.

TPNH is the preferred hydrogen donor for all of the substrates tested with the particulate enzymes, and it is questionable whether DPNH can function at all (TABLE 4). The 2 sets of enzymes are, therefore, very much alike; a comparative summary of some of their properties is shown in TABLE 5.

Biological Considerations

From the preceding discussion we have seen that TPNH is the hydrogen donor for steroid double-bond reduction (in mammalian organisms) regardless of whether the 5α or 5β dihydro product is formed. An important question concerning these reactions *in vivo* obviously is: What is the effect of the intracellular reduced-TPN concentration on the rate of steroid saturation? This raises the further question of whether, *in vivo*, the steroid-reducing enzymes are saturated with reduced pyridine nucleotide. It is very difficult to approach these problems from a consideration of total intracellular reduced-TPN concentration because of compartmentalization of both the nucleotide and the enzymes. Recent work in this laboratory[23] has indicated that, in fact, the intracellular-TPNH concentration is rate-determining for steroid reductions by either the 5α or 5β enzymes. Some of these experiments are illustrated in FIGURE 5. A corollary of these observations is that the entire process of steroid metabolism by liver is regulated by the concentration of intracellular TPNH available for 4–5 double-bond reduction.

TABLE 5
COMPARISON OF PROPERTIES OF THE STEROID REDUCTASE

	Soluble	Microsomal
Product formed	5β	5α
Number of enzymes	Many	Many
Substrate specificity	High	High
Hydrogen donor	TPNH	TPNH
Localization	Liver	Liver
Equilibrium	Irreversible reduction	Irreversible reduction
Substrate affinity	High $K_{m(\text{cortisone})} = 4.7 \times 10^{-5}$	High $K_{m(\text{cortisone})} = 8.1 \times 10^{-5}$

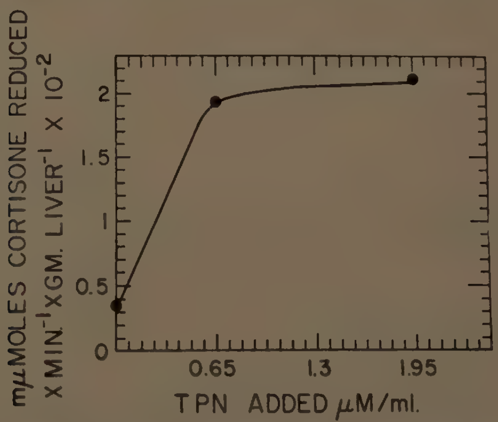


FIGURE 5. The reaction mixture contained 20 μmoles tris(hydroxymethyl)aminomethane (*p*H 7.4), 0.2 ml. liver homogenate, 0.3 μmole cortisone, a TPNH-generating system, and TPN added as indicated. The mixture had a total volume of 2 ml. and was incubated for 5 min. at 37° C.

It must be borne in mind, however, that TPNH concentration is not the only determinant of this rate since, of course, it is also a function of both steroid and enzyme concentration, and factors affecting either of these will also affect the rate of the reaction. An interesting example is the finding of Peterson *et al.*[8] that the rate of hydrocortisone reduction, but not that of cortisone, is diminished in patients with liver disease. This is best explained by the observation mentioned above that different enzymes are, in fact, involved in cortisone and hydrocortisone reduction, in that the hydrocortisone enzyme is more labile in the diseased condition than is the cortisone enzyme. In this case then, it is obviously not the reduced pyridine nucleotide concentration that is responsible for this alteration in rate.

An important source of TPNH in liver cells is the oxidation of glucose-6-phosphate (G-6-P) by TPN to form 6-phosphogluconolactone and TPNH catalyzed by the enzyme G-6-P dehydrogenase. Glock and McLean[24] found that the level of G-6-P dehydrogenase in liver could be increased by the administration of thyroid hormone to rats. We have confirmed this,[23] and have shown further that such an increase can enhance the rate of steroid double-bond saturation by increasing the steady-state concentration of reduced TPN available for the reduction. This is illustrated by experiments that show[23] that the rate of steroid reduction is more rapid in thyroxine-treated than in normal rats and that this inequality can be removed by providing more TPNH to the normal animal in the form of a TPNH-generating system.

The critical role of TPNH in regulating steroid degradation by the liver is interestingly parallel to the control of corticoid biosynthesis in the adrenal by the same coenzyme.[25] The latter situation derives from the fact that steroid hydroxylation reactions in the adrenal are numerically the most important steps in the biosynthesis of the adrenal hormones, and each of these requires TPNH.[26]

Both synthesis and degradation are regulated, therefore, by TPNH levels in the appropriate organs. A situation where the amount of available reduced pyridine nucleotide is increased in both sites (in rats) is thyrotoxicosis, induced by the administration of thyroxine. Liver G-6-P dehydrogenase is increased, as previously mentioned, and the same enzyme is elevated in the adrenal.[27] This situation should result in an increase in both synthetic and degradative rates of the cortical hormones.

The finding of Peterson[28] that thyrotoxic patients show a faster corticoid turnover rate (that is, increase in both synthesis and degradation) with no change in the steady-state concentration is entirely consistent with the formulation outlined.

Up to this point the discussion has been concerned with factors that can affect the enzymatic inactivation of the cortical hormones. The following will consider the converse situation—that is, the influence of steroid degradation on other metabolic processes.

Upon reduction of an α,β-unsaturated steroid by either the 5α- or 5β-steroid reductases, 1 mole of TPN is produced at the expense of an equal amount of TPNH. Wenner *et al.*[29] have shown recently that the rate of reoxidation of TPNH limits the rate of G-6-P oxidation by the oxidative pathway, and that synthetic oxidizing agents (such as dyes) can accelerate G-6-P metabolism. It should be possible to couple steroid reduction with G-6-P oxidation according to the equation:

$$\begin{array}{c}
\text{2 steroid} + \text{2 TPNH} + \text{H}^+ \rightarrow \text{2 dihydrosteroid} + \text{2 TPN} \\
\text{G-6-P} + \text{2 TPN}^+ \rightarrow \text{pentose-P} + \text{CO}_2 + \text{2 TPNH} + \text{2 H}^+ \\
\hline
\text{2 steroid} + \text{G-6-P} \rightarrow \text{2 dihydrosteroid} + \text{pentose-P} + \text{CO}_2
\end{array}$$

Here a steroid is used as an oxidizing agent for TPNH.

Some experiments designed to test such a coupling have been carried out by Yielding; one of these is illustrated in TABLE 6. The addition of reducible steroid stimulates the rate of glucose-6-phosphate oxidation in either a whole homogenate of liver or an ultracentrifuged supernatant fraction of the same organ. This response, although striking, cannot be considered to be truly hormonal since, of course, the steroid is acting as a stoichiometric oxidizing agent for reduced TPN, and physiological considerations dictate that the steroids must act in a catalytic fashion. If the enzyme described by Levy and Talalay[17] were present in mammalian tissue, then the steroid could function catalytically as follows:

$$\text{steroid} + \text{TPNH} + H^+ \rightarrow \text{dihydrosteroid} + \text{TPN}$$

$$\text{dihydrosteroid} + \text{dye} \rightarrow \text{steroid} + \text{dye } H_2$$

In this situation, unsaturated steroid would act catalytically to promote the oxidation of reduced pyridine nucleotide and thereby regulate the rate at which such processes as G-6-P oxidation occur. Unfortunately, no such unsaturating enzyme has been found in mammalian tissue. However, an analogous system exists in plants, where the irreversible reduction of glyoxylic acid to glycolic acid[16] is catalyzed by a pyridine nucleotide–linked reductase. A flavin enzyme, glycolic acid oxidase, then reoxidizes glycolic acid to glyoxylic acid, and the net result is that either glycolic acid or glyoxylic acid can act catalytically to promote the oxidation of DPNH. It may be that in plants these acids act as regulators for various metabolic processes by the same mechanism as is suggested here for α,β-unsaturated steroids.

TABLE 6
EFFECT OF CORTISONE ON C^{14}-LABELED G-6-P OXIDATION*

Addition	cpm recovered as CO_2
None	355
Cortisone (1×10^{-4} M)	805

* The enzyme was a dialyzed supernatant of rat liver. In addition, the reaction mixture contained (final concentration): TPN, 2×10^{-4}; $MgCl_2$, 2×10^{-3}; nicotinamide, 10^{-3}; tris(hydroxymethyl)aminomethane (pH 7.4), 0.02; and G-6-P, 1×10^{-4}, with a specific activity of 8.0×10^3 cpm/μmole. The mixture had a total volume of 5 ml. and was incubated for 30 min. at 37° C.

Summary

The characteristics of the enzymatic reduction of steroid double bonds have been considered.

Two series of enzymes present in mammalian liver can carry out this reaction. One of these, in the soluble fraction, produces the 5β isomer; the other, localized in microsomes, catalyzes the formation of the 5α isomer.

Many of the characteristics of these enzymes are similar.

TPNH concentration controls that rate of steroid reduction by liver.

In turn, steroid reduction may act (in a model system) to reoxidize TPNH to TPN and, thereby, to accelerate metabolic processes dependent on TPN.

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METABOLISM OF ADRENOCORTICOSTEROIDS IN MAN

R. E. Peterson
Cornell University Medical College, Ithaca, N. Y.

More than 40 steroids have been isolated from the adrenal cortex, and others await isolation and identification. A multitude of additional steroid metabolites has been found in the blood and urine. From studies of adrenal-vein blood in various animals, it appears that cortisol, corticosterone, and aldosterone are the major corticosteroid secretory products.[1-5] In man, cortisol represents the major glucocorticosteroid, and aldosterone very probably represents the major minerocorticosteroid. Corticosterone, which man secretes in small quantities, is of interest because in certain species (for example, rodents) it is the major adrenal steroid secreted. It is the purpose of this paper to summarize our present knowledge of the metabolism of these three natural adrenocorticoids: cortisol, corticosterone, and aldosterone.

Within the past few years a great deal has been learned about the metabolic fate of these adrenocorticoid hormones. This has been made possible by the development of improved analytical methods for measurement of the steroids and by the introduction of practical methods for the production of steroids containing the radioactive isotopes of carbon and hydrogen. This acquisition of fundamental knowledge concerning the fate of the corticosteroids in the body has made possible an elucidation of factors that affect two important parameters of adrenocortical activity—the plasma level of the adrenocorticosteroids and their rate of production *in vivo*.

The circulating plasma level of the steroids is an important index of adrenocortical activity if we accept the rather simple premise that the response of the target tissue and the biological activity of the steroid are directly related to the steroid concentration in the extracellular fluid. It is usually not possible to measure the steroid concentration at the sites of action (extracellular fluid). Since the plasma is the physiological means of exchange, the steroids must pass through the plasma to get to the tissues; therefore, an elevation in the plasma steroid level indicates that the steroid concentration at the site of action is also elevated.

In 50 normal adult subjects the plasma cortisol level, as determined by a modified Silber-Porter method,[6] ranged from 6 to 25 μg. per cent, with a mean of 13.3. In 20 normal subjects the more selective isotopic-dilution method of assay demonstrated a range of 5 to 20 μg. per cent, with a mean of 11.5. In 30 normal subjects the plasma level of corticosterone, as determined by an isotope-dilution or double-isotope dilution derivative method,[8] ranged from 0.4 to 2.0 μg. per cent with a mean of 1.0. In 8 normal subjects the plasma aldosterone level, based on determinations by a double-isotope dilution derivative assay,[8] ranged from 0.03 to 0.08 μg. per cent, with a mean of 0.05 (TABLE 1).

In establishing the relationship between the plasma steroid level and the biological activity of the hormone, cognizance must be taken of at least 2 additional factors:

First, the range of normal plasma steroid levels listed above represents the concentrations of steroids found in the plasma between 7 and 9 A.M. Although the fasting state does not appear to play an important role in influencing the steroid levels, it must be remembered that the plasma levels of cortisol[9] and corticosterone[7] do show a very definite diurnal fluctuation. No investigation of a possible diurnal variation in plasma aldosterone has been made. Plasma levels of cortisol and corticosterone are highest between 6 and 9 A.M. and decline slowly thereafter, dropping to a minimum between midnight and 4 A.M. Thus it is conceivable that an alteration in the magnitude of the diurnal rhythm may be an important consideration in interpreting the physiological significance of the circulating level of steroid hormone. The absence of a P.M. decline in steroid concentration may contribute to the production of a state of hypercorticism.

Second, it is now known that cortisol, corticosterone, and aldosterone exist in the blood in 2 different physiochemical states—free or unbound in aqueous solution, and bound to protein.[10-14] Conventional chemical assay methods for plasma steroids measure both the unbound and the protein-bound steroid. With plasma cortisol and corticosterone concentrations within the normal range, the fraction of nonprotein-bound steroid is extremely small—less than 5 per cent of the total. The protein or proteins (called "transcortin"[15]) that bind and transport the steroid appear to reside in the α-globulin fraction and have a great avidity for cortisol and corticosterone. The protein appears to be almost completely saturated at normal or physiological concentrations of cortisol but, at concentrations above normal (saturation), cortisol and corticosterone appear to bind to serum albumin, which has less avidity for these steroids. With serum albumin, 70 to 80 per cent of the steroid is protein-bound.

TABLE 1
PLASMA STEROID LEVELS IN NORMAL SUBJECTS*

	Cortisol		Corticosterone		Aldosterone
	PNH (50)	ID (20)	ID (20)	IDr (10)	IDDr (8)
Range	6–25	5–20	0.4–2.0	0.4–2.0	0.03–0.08
Mean, s.d.	13.3 ± 3	11.5 ± 2.5	1.1 ± 0.4	1.0 ± 0.4	0.05 ± 0.01

Key: PNH, phenylhydrazine-reacting chromogens; ID, isotope-dilution assay; IDr, double-isotope derivative assay; IDDr, double-isotope dilution derivative assay.

* All figures are in micrograms per cent; those in parentheses indicate the number of subjects in each group.

The importance of the steroid protein-binding resides in the effect this may have on the distribution (vascular → extravascular → intracellular), transport, excretion and, thus, the biotransformation of the steroid. The extravascular or tissue concentration of cortisol and corticosterone will depend as much upon the concentration and properties of the plasma protein or proteins with which it is bound as upon the concentration of the steroid. The concentration of steroid is normally lower in the extracellular fluid than in the plasma.[16, 17]

If the transcortin-bound steroid represents an inactive transport complex, then it is likely that it is only the nonprotein-bound steroid that is biologically active and capable of diffusion into the extravascular space and cells. The transcortin would normally be expected to protect the tissues from abnormally high levels of cortisol, yet, under circumstances (stress) requiring a sudden need for higher tissue levels of steroid, these requirements could be met readily by only moderate elevations (and increased adrenocortical secretion of steroid) of the plasma cortisol above the saturation level (20 μg. per cent).

A reduction in the concentration of transcortin, or in the protein-binding sites available for cortisol, could be responsible for a Cushing's syndrome in patients who appear to have normal plasma cortisol levels as determined by the usual chemical methods. In late pregnancy the presence of elevated cortisol levels without an associated hyperadrenocorticism may be the consequence of increased protein-binding or an increase in the number of binding sites for cortisol. It is during the third trimester of pregnancy that the plasma estrogen levels become elevated and, since administration of exogenous estrogen produces an elevation in the plasma level of cortisol and the steroid protein-binding of cortisol,[18] it is reasonable to assume that the protein-bound cortisol may be increased during the later part of pregnancy; this has now been reported.[19] In the normal subject treated with estrogens, the elevated plasma cortisol level (50 to 60 μg. per cent) is not associated with any sign of hyperadrenocorticism, and the plasma cortisol is protein-bound to the extent of more than 95 per cent.[13]

Aldosterone appears to be bound by serum albumin, since over a wide range of concentrations, using either human serum albumin or undiluted plasma,[13, 19] 70 to 80 per cent of this steroid is bound. Thus, at normal plasma aldosterone concentrations, a larger fraction of the total circulating aldosterone is available to the tissues.

Steroid-protein binding may play some role in preventing the steroid from being filtered through the glomeruli of the kindey, less than 1 per cent of the cortisol produced daily by the adrenal being excreted unchanged in the urine, and none appearing in the bile.[20]

The plasma protein that binds and transports the steroids may also play a role in protecting them from excessively rapid transformation by the liver enzymes, and may thus influence the rate at which they are metabolized. Infused adrenocorticosteroids do disappear rapidly from the circulation. The rate of disappearance (or metabolism) of both cortisol and corticosterone has been found to vary directly with the dose of infused steroid.[18, 21] With the infusion of 50 to 400 mg. of cortisol or 50 to 200 mg. of corticosterone, the biological half time of the plasma cortisol was about 110 min.; that of the corticosterone, 80 min.; and the rate of metabolism was proportional to concentration. With the infusion of trace quantities of steroid, both cortisol and corticosterone are metabolized at a more rapid rate—$t_{1/2}$ = 85 and 65 min., respectively. Calculations of the "apparent volume of distribution" following the infusion of trace and pharmacological doses also yielded different results. With the trace dose, the apparent volume of distribution was one quarter to one fifth as large.[22] Infused aldosterone is metabolized at a more rapid rate—$t_{1/2}$ = 50 min. It is not known if the rate of metabolism is delayed when doses greater than 1 mg. are administered (TABLE 2).

The cause of these differences in rates of metabolism of the trace and pharmacological doses is not clear, but they cannot be explained on the basis of different rates of metabolism of labeled and unlabeled steroid. It seems likely that differences in the fraction of free and protein-bound steroid at physiological (trace) and pharmacological levels may contribute to the differences in rates of disappearance of the steroids from the plasma. With the larger doses of infused steroid and the higher plasma steroid levels (in the range of 50 to 500 μg. per cent), a larger fraction of nonprotein-bound steroid is available for diffusion into the extravascular space. A slower rate of removal of the plasma steroid by diffusion and a more rapid rate of removal incident to metabolsim will result in a slower biological half time. Also, re-entry of the steroid into the intravascular compartment from a large extravascular pool could result in a delayed disappearance of the steroid from the vascular pool. Thus, even in the absence of any appreciable excretion, the rate of disappearance of the steroid may not always be a reliable index of its rate of metabolism, even though the rate of decline in plasma concentration represents a first-order function.

TABLE 2

BIOLOGICAL HALF TIMES OF PLASMA STEROIDS*

	Normal	Cirrhosis	Thyrotoxicosis
Cortisol	110 (80)	300	60
Corticosterone	80 (60)	90	40
Aldosterone	(50)	(80)	—
Cortisone	30	35	12
Δ^1-Cortisone	60	—	—
Δ^1-Cortisol	200	240	—
Δ^1-9α-Fluoro, 16α-CH_3-cortisol	200	—	—
9α-Fluorocortisol	90	95	—
Δ^1-9α-Fluorocortisol	100	100	—
Dihydrocortisol	30	40	—
Tetrahydrocortisol	35	40	—

* All figures are in minutes; those in parentheses were obtained after infusion of trace dose, and those within each group (normal, cirrhosis, thyrotoxicosis) represent the results of studies in a single subject.

There appears to be no significant localization of the steroids in the tissues or storage depots (other than the plasma proteins), and thus they are not well protected from rapid metabolic transformation by the liver. Excretion via the urine plays no important role in influencing the rate of disappearance of the steroids from the plasma. There are, however, various drugs and disease states that change the rate of disappearance of cortisol from the plasma,[18, 23, 24] presumably by altering the capacity of the liver to metabolize the circulating steroid. The rate of metabolism of cortisol is delayed in liver disease, myxedema, pregnancy, old age, and starvation. Estrogen therapy and high doses of salicylate for long periods of time also produce a delay in the disappearance of infused cortisol. The metabolism of cortisol is increased in thyrotoxicosis and, in addition, has recently been reported to be increased in some patients with spontaneous hypoglycemia.[25] It has been possible to demonstrate in rats that an increased rate of steroid inactivation by liver homogenates follows thyroxin administration. The livers of the thyroxine-treated animals have been shown to contain an increased level of TPNH and of the 5α, dehydrogenase liver-microsome enzymes.[26]

In both myxedema and thyrotoxicosis the alteration in corticosterone metabolism parallels that of cortisol.[24] In liver diseases the metabolism of corticosterone and aldosterone does not seem to be significantly altered from the normal.[18]

Studies of the disappearance of the synthetic and biologically active steroids from the plasma have been carried out with infusions of pharmacological quantities of the steroids. Both prednisolone and dexamethasone disappear from the circulation more slowly than cortisol ($t_{1/2}$ = 150 to 220 min.) and 9α-fluorocortisol and 9α-fluoroprednisolone are metabolized more rapidly than cortisol ($t_{1/2}$ = 70 to 100 min.). Prednisone, like cortisone, is metabolized much more rapidly than cortisol; however, in large measure both of these steroids are rapidly converted *in vivo* to prednisolone and cortisol, respectively. Thus, while there does not appear to be a good correlation between the glucocorticoid and minerocorticoid activities of the steroids and their rates of metabolism, it may be necessary to study the infusion of trace quantities of the synthetic steroid before a valid evaluation of rates of *in vivo* metabolism of the steroids can be made.

The rate of metabolism of the infused steroids and the plasma steroid concentration give no information regarding the rate of secretion of steroids by the adrenal cortices. An elevated plasma level of steroid does not necessarily indicate increased secretion; however, a normal plasma level in the presence of an increased rate of metabolism suggests increased secretion, and a normal plasma level in the presence of a decreased metabolism suggests a decreased secretion of steroid.

The rate of secretion of the steroids by the adrenal cortices is an important index of the functional activity of the adrenal cortex, especially for purposes of evaluation of adrenal pathology. For many years urine steroid assays have been used to evaluate the level of activity of the adrenal cortices. Initially, urine 17-ketosteroid assays were employed for this purpose; however, their excretion is primarily a measure of the capacity of the adrenal cortices to secrete C-19 androgenic steroids and may not always reliably reflect adrenal secretion of gluco- or minerocorticoid. Within the past 6 years, clinically useful methods have been developed for measuring a fraction of the urinary metabolites of cortisol. These methods measure 20 to 40 per cent of the cortisol metabolites and may yield only an approximation of adrenal glucocorticoid secretion.[18] The results of urine corticoid assays do not serve as a reliable guide to the circulating plasma cortisol level, and only a very small fraction of the steroid measured by these methods is cortisol. They are used to best advantage as an index of the rate of production of cortisol; a decreased concentration of urinary steroid metabolites usually representing decreased adrenal production. The urine levels of aldosterone also probably represent more accurately a reflection of aldosterone production rather than a guide to the plasma aldosterone level.

In order to resolve the uncertainties associated with estimations of steroid production from determinations of a fraction of the urine steroid metabolites of the parent compound, we have utilized the labeled (radioactive) steroids to obtain a more quantitative measure of adrenal cortical activity. We have measured adrenal secretion rates by 2 different methods. In the first, (the kinetic or rate method),[22] we were able to measure a quantity of the circulating steroid termed the miscible-steroid pool. This is the steroid that is capable of prompt and homogeneous mixing with an injected labeled steroid of the same species. If the quantity of steroid contained in the body in a miscible state and the value of its enrichment with isotope are given some designation and if, then, the assumption is made that the rates of entry and exit from the pool are equal and constant and the quantity within the pool is constant, one may show a logarithmic relationship between the isotope concentration and time. The logarithm of the isotope concentration plotted against time will give a straight line with a slope equal to the fraction of the pool replaced per unit time and with an intercept equal to the logarithm of the isotope concentration at the moment of mixing at time zero. The validity of this derivation is confirmed by experimental results obtained in the normal subject.

Essentially linear relationships are obtained when the logarithm of the isotope concentration in the plasma is plotted against time after the intravenous injection of cortisol in tracer amounts. In most of these experiments the cortisol was labeled with carbon-14; however, similar results have been obtained with tritium-labeled cortisol and, more recently, with tritium-labeled corticosterone. From the slopes and intercepts of these plots one can calculate the magnitude and the rate of turnover of the miscible pool of cortisol, corticosterone, and aldosterone.[18]

The magnitude of the miscible pool is computed as the quantity of steroid that dilutes the injected isotopic steroid at the moment of injection. The following data have been obtained for the steroid pools in normal subjects: cortisol, 1.5 mg.; corticosterone, 200 μg.; and aldosterone, 10 μg.

In addition to the kinetic method for measuring the rate of turnover of adrenal steroids, we have employed another procedure that utilizes the principle of isotope dilution of the injected labeled steroid by one or more of its urinary metabolites.[18, 27-29] If a trace quantity of a radioactivity-labeled steroid is injected intravenously, it will enter, like the endogenous parent steroid, equally into all of the metabolites of the steroid (both known and unknown) and will appear in the urine. The labeled steroid and its metabolites are diluted by the corresponding unlabeled steroid and its metabolites, and the extent of this dilution can then be determined by measuring the isotope concentration of the steroid or of one or more of its metabolites. Knowledge of the specific activity of the injected steroid and the specific activity of the isolated steroid, plus knowledge of the total time of the urine collection after administration of the labeled steroid, makes it possible to calculate the rate of steroid secretion.

Table 3 shows the turnover-rate data for cortisol, corticosterone, and aldosterone in the normal subject. This type of study has been applied to normal subjects, both before and after treatment with drugs or before and after various experimental procedures, and in patients with diverse diseases. The differences in the results of the turnover-rate measurements by the kinetic or rate method and the urine specific-activity method are a reflection of the diurnal variation in the rate of secretion of cortisol and corticosterone. The rates of secretion of cortisol and corticosterone have been found to be decreased in patients with myxedema and cirrhosis, and after estrogen and long-term salicylate therapy. These are the same conditions under which the rate of metabolism of infused cortisol and corticosterone is delayed. In these same conditions the urine steroid level is low, but the plasma steroid level is normal. In patients with thyrotoxicosis the secretion rate as well as the rate of metabolism of infused cortisol and corticosterone are increased; however, the urine steroid level is usually elevated, whereas the plasma steroid level is normal. A low sodium intake, in addition to elevating the plasma and urine levels of aldosterone, will produce a two- to threefold increase in the rate of secretion of aldosterone.

These studies of the various indices of steroid metabolism (plasma and urine steroid concentration, rate of metabolism, and rate of secretion of steroid) in the normal subject and in patients with various diseases have shown that alterations in the rates of adrenal-steroid secretion are reflected by alterations in the rate of metabolism of the steroids, and in the urine steroid concentration. They have also shown that changes in the rate of steroid secretion are not always reflected by changes in the plasma steroid level. The plasma steroid level must be interpreted in terms of the diurnal fluctuation in plasma steroid concentration and the physicochemical state of the plasma steroid.

TABLE 3

RATE OF TURNOVER OF STEROIDS IN NORMAL SUBJECT

	Pool mg.	K		S.A. mg./day	Urine steroids (mg./day)		
		mg./hr.	mg./day		C	TH	Free
Cortisol, A.M.	1.5	0.83	20	15.6	7.0	6.2	0.04
Cortisol, P.M.	0.5	0.40	8	15.0	6.5	—	
Corticosterone	0.2	0.17	4.1	2.0	—	0.7	0.005
Aldosterone	0.01	0.006	0.14	0.35	0.007	—	0.0005

Key: K, kinetic method; S.A., specific activity of urine metabolite; C, chemical assay, fraction of metabolites; TH, total 11-hydroxy, 20-keto, tetrahydro plus 11, 20-keto, tetrahydro metabolites; and Free, fraction of injected steroid excreted.

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EFFECTS OF ANTI-INFLAMMATORY STEROIDS ON ELECTROLYTE METABOLISM*

Grant W. Liddle

Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

With the advent in 1948 of cortisone as a therapeutic agent it soon became apparent that the supraphysiological dosages required in the management of certain inflammatory and allergic disorders were attended by significant alterations in electrolyte metabolism.[1] Sodium retention and potassium depletion were the most prominent derangements of electrolyte metabolism during cortisone therapy. In some cases these effects were accompanied by the clinical manifestations of edema, hypertension, muscular weakness, and cardiac arrhythmias. Metabolic studies demonstrated that by restriction of sodium intake one could minimize both the tendency to accumulate sodium and the tendency to waste potassium.[2] Conversely, by raising the intake of potassium it was possible not only to minimize potassium depletion, but to prevent sodium retention as well.[3] It came to be regarded as good medical practice to prescribe sodium restriction and potassium supplementation for patients receiving more than 75 mg. of cortisone per day.

Electrolyte-regulating activity is not necessarily correlated with anti-inflammatory activity of steroids, however, and an important advance in corticotherapy has occurred during the past 4 years with the development of several synthetic steroids that, compared with cortisone, exhibit enhanced anti-inflammatory potency without commensurate enhancement of electrolyte-regulating potency. Serious aberrations of electrolyte metabolism are now rarely encountered as a result of corticotherapy if care is exercised in the selection of anti-inflammatory agents.

Mechanisms Through Which Corticosteroids Affect Electrolyte Metabolism

Although steroids influence electrolyte metabolism in a number of ways, their most important effects are exerted upon renal function. It is impossible to alter the excretion of one electrolyte without concomitant alteration of others. For the sake of orientation, however, steroids might be regarded from the standpoint of their effects on Na^+ excretion. Depending upon the type of steroid administered and the physiological status of the patient, it is possible to induce either retention or loss of Na^+.

Steroids that cause Na^+ retention do so by increasing the inherent tendency of the renal tubules to reabsorb Na^+ from the glomerular filtrate by means of a cation-exchange process in which K^+ and H^+ are secreted into the tubular urine.[4-6] Cl^- reabsorption tends to parallel that of Na^+. As NH_3 is secreted by the tubules, it combines with H^+ ion in the tubular urine, where it remains "trapped" as NH_4^+. NH_4^+ excretion tends to parallel H^+ excretion. In general, therefore, steroids that induce Na^+ retention also induce retention of Cl^- and increased excretion of K^+, H^+, and NH_4^+.[6, 7]

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These effects are well illustrated in studies of the naturally occurring mineralocorticoid aldosterone. As illustrated in FIGURE 1, the intravenous administration of aldosterone to adrenalectomized dogs results in acute retention of Na^+ and loss of K^+ without any significant change in glomerular filtration rate (GFR). As illustrated in FIGURE 2, the administration of aldosterone to

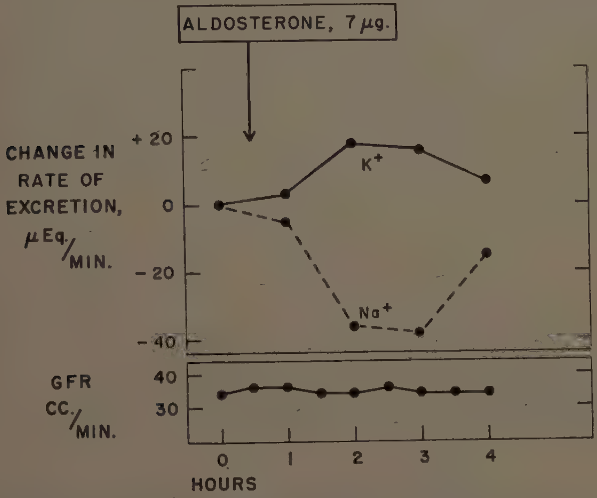

FIGURE 1. The acute renal response to aldosterone (7 μg.) administered intravenously to an adrenalectomized dog. No significant change in glomerular filtration was observed; the changes in Na^+ and K^+ excretion were attributed to an effect of aldosterone on renal tubular cation exchange.

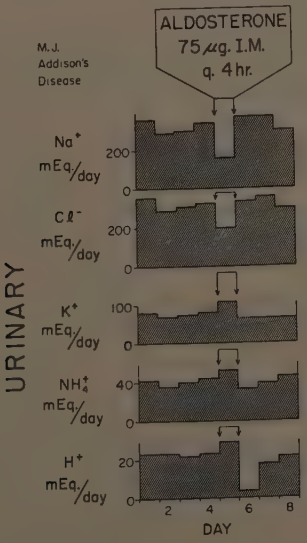

FIGURE 2. Effects of aldosterone administered intramuscularly in dosages of 75 μg. every 4 hours to a patient with Addison's disease who was maintained on constant dietary intake. The altered pattern of urinary electrolytes was attributed to the action of aldosterone upon the renal tubules.

a human subject results in decreased renal excretion of Na^+ and Cl^- and increased excretion of K^+, H^+ (titratable acid), and NH_4^+. Since Na^+ reabsorption and K^+ excretion are thought to be consequences of the same cation-exchange process, it should not be surprising that steroids that cause Na^+ retention also cause K^+ depletion.

Steroids that cause an increase in Na^+ excretion may do so by any of 3 mechanisms: (1) by inhibiting the tendency of aldosterone to promote renal tubular cation exchange, (2) by increasing GFR, or (3) by inducing a decrease in the secretion of aldosterone.

Aldosterone antagonism. During the past 5 years evidence has been adduced indicating that, if certain steroids are administered in the presence of aldosterone, the effectiveness of the latter is diminished. This phenomenon is referred to as "aldosterone antagonism," a term that conveys no implication as to the intimate nature of the process. The clearest example of aldosterone antagonism is offered by the steroid-17-spirolactones,[7-10] a series of synthetic compounds that have little or no effect upon electrolyte excretion in adrenalectomized animals. When administered to animals with intact adrenals, however, or to adrenalectomized animals maintained on aldosterone, the "spirolactones" tend to abolish the usual effects of aldosterone upon electrolyte excretion. In the presence of aldosteronelike steroids, then, the characteristic effects of the spirolactones are those of increased excretion of Na^+ and Cl^- and decreased excretion of K^+, H^+, and NH_4^+.

It is probable that other steroids too may cause increased Na^+ excretion through the process of aldosterone antagonism. Landau *et al.*[11, 12] have presented strong evidence that progesterone in large dosages acts in this manner.

Effects of steroids on glomerular filtration rate. When a large acute increase occurs in this rate (GFR), regardless of the cause, it is often accompanied by a parallel increase in excretion of Na^+ and other electrolytes. The anti-inflammatory steroids, given in adequate dosage, induce acute increases in GFR. In considering the conditions under which steroids are assayed for electrolyte-regulating activity, it should be noted that the dog and the rat are probably more susceptible than man to agents that alter GFR. Furthermore, patients or animals with a deficiency of hydrocortisonelike steroids are probably more susceptible than normal to the GFR effects of anti-inflammatory steroids. The acute effects of hydrocortisone upon GFR, Na^+ excretion, and K^+ excretion of the adrenalectomized dog are illustrated in FIGURE 3. The increase in Na^+ excretion tends to parallel the increase in GFR, and it is reasonable to suppose that the former is a consequence of the latter. It is important to note that the percentage increase in excretion of K^+ exceeds the percentage increase in excretion of Na^+. Such a change in the electrolyte pattern of the urine suggests that, in addition to its effect on GFR, the steroid exerts an aldosteronelike effect upon renal tubular function. Experience has shown that, if anti-inflammatory steroids are to be assayed for their aldosteronelike activity in the adrenalectomized dog, it is better to rely upon some function such as the decrease in the urinary Na^+/K^+ ratio rather than upon a decrease in Na^+ excretion alone.[13] In the adrenalectomized dog (or rat) an anti-inflammatory steroid such as hydrocortisone can act like aldosterone in increasing the tendency of the renal tubules to reabsorb Na^+ in exchange for K^+ and H^+, while the animal may continue to exhibit a net loss of Na^+ because the steroid *also* acts to increase GFR. In the human subject who has no hydrocortisone deficiency to start with, hydrocortisone is not so likely to induce an acute increase in GFR; the steroid does increase tubular reabsorption of Na^+, however, and the usual net effect is a decrease in Na^+ excretion.

Effects of anti-inflammatory steroids upon aldosterone secretion. A third possible mechanism through which the anti-inflammatory steroids may induce Na^+ loss is that of indirect suppression of aldosterone secretion. Several studies[14-16] have indicated that aldosterone secretion is not governed by the pituitary and that suppression of ACTH-secretion has little effect upon this particular steroid. In normal individuals in whom aldosterone secretion is high in response to a low sodium diet, the anti-inflammatory steroids have little effect on aldosterone secretion. In diseases such as nephrosis, cirrhosis, or congestive heart failure, in which aldosterone secretion is high in response to impaired circulation, the anti-inflammatory steroids occasionally may have a beneficial effect upon the underlying disease process and, thereby, indirectly bring about a decrease in aldosterone secretion accompanied by diuresis. Luetscher has demonstrated this phenomenon in patients with nephrosis.[17] Vesin has written extensively of decreases in aldosterone secretion during prednisone therapy in patients with congestive heart failure [18] and cirrhosis,[19] but in our own laboratory little success has been experienced in treating congestive heart failure or cirrhosis with anti-inflammatory steroids. Theoretically, the patient with congestive heart failure due to acute rheumatic pancarditis is one in whom treatment with anti-inflammatory agents might improve cardiac function so as to correct the abnormal stimulus to aldosterone secretion.

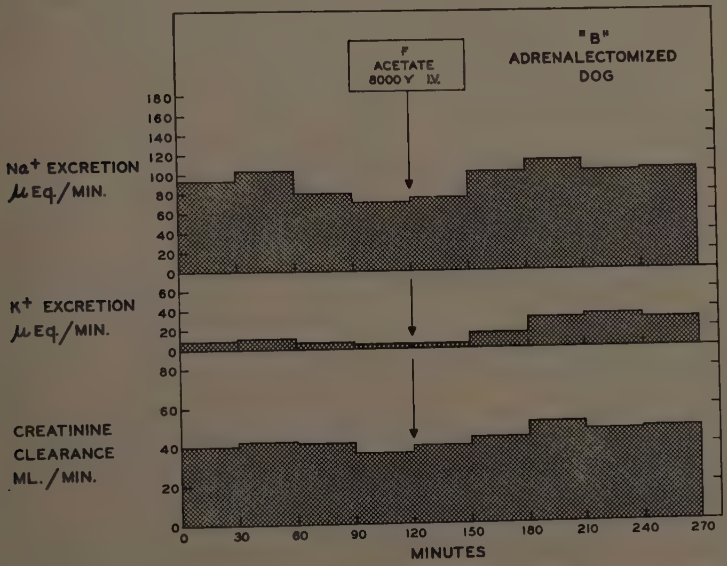

FIGURE 3. The acute renal response to hydrocortisone acetate (8 mg.) administered intravenously to an adrenalectomized dog. A significant increase in glomerular filtration rate was accompanied by a parallel increase in the rate of Na^+ excretion.

Multiple effects of a single anti-inflammatory steroid. As suggested above, it is possible for a single steroid to exert multiple actions influencing Na^+ excretion. Cortisone, for example, mimics aldosterone in its effect upon renal tubular cation exchange, causing Na^+ retention and K^+ loss. However, there is evidence that cortisone may also be effective in increasing GFR, in antagonizing the tubular action of more potent aldosteronelike steroids, and in correcting some of the pathological conditions leading to hypersecretion of aldosterone. It should not be surprising, therefore, if the net effect of cortisone were sometimes Na^+ retention and at other times Na^+ loss, depending upon which of the above effects dominated a particular physiological situation. Almost ten years ago Thorn *et al.*[20] invoked the concept of competitive inhibition to explain their observation that cortisone induced Na^+ excretion in the Addisonian patient maintained on desoxycorticosterone acetate (DOCA). Such a concept is difficult to prove in the case of cortisone, however, since this steroid is known to increase GFR. In other words, either of two postulated mechanisms for Na^+ loss might be invoked to explain these authors' observations: (1) cortisone could have induced Na^+ loss by increasing glomerular filtration of Na^+, or (2) cortisone, a steroid only weakly active in promoting tubular reabsorption of Na^+, might have hindered the renal tubular action of DOCA, a potent agent in promoting Na^+ reabsorption.

TABLE 1

MECHANISMS THROUGH WHICH CORTICOSTEROIDS INFLUENCE NA^+ EXCRETION

Na^+ retention
  - Increased tubular cation exchange (aldosteronelike action)

Na^+ loss
  - Aldosterone antagonism (spirolactonelike action)
  - Increased GFR (property of anti-inflammatory steroids)
  - Correction of pathological stimulus to hypersecretion of aldosterone

In his classic study of primary aldosteronism[21] Conn noted that hydrocortisone induced a loss of Na^+ and Cl^- in the urine, and he postulated that hydrocortisone "acts as an antagonist to aldosterone with respect to the direction in which the sodium ion moves across cell membranes." Studies of Na^+ and K^+ secretion in sweat and saliva did not illuminate this point, and data concerning GFR were not presented. Once again, therefore, it is possible to invoke either the concept of aldosterone antagonism or that of increased filtration of Na^+ to explain the observed effect upon Na^+ excretion; perhaps both mechanisms were operative.

Potassium loss unrelated to aldosteronelike action of steroids. All of the known anti-inflammatory steroids tend to cause wasting of protein, with resultant negative balances of nitrogen, phosphorus, and potassium.

An additional action of anti-inflammatory steroids upon potassium metabolism has been suggested by Bartter and Fourman[22] on the basis of their observation that on the initial day of treatment with hydrocortisonelike steroids there occurs an increase in K^+ excretion without concomitant Na^+ retention, without a fall in serum K^+ concentration, and without concomitant loss of nitrogen. These authors concluded that the hydrocortisonelike steroids caused a release of potassium from cells, with a consequent increase in K^+ excretion.

Through either of these mechanisms there may occur a decrease in total body K^+, which is independent of any tendency to retain Na^+ or to develop hypokalemia.

Compensatory mechanisms. The homeostatic mechanisms available to the body are such that the effects of an exogenous steroid upon electrolytes tend to be self-limiting. Some obvious mechanisms through which this adaptation may occur are those concerned with aldosterone secretion and GFR. A steroid that, like aldosterone, causes Na^+ retention will tend to cause expansion of extracellular fluid volume and thereby initiate circulatory changes that result in decreased aldosterone secretion and increased GFR; the latter conditions facilitate loss of Na^+ in the urine. A steroid that, like the spirolactones, causes Na^+ excretion will tend to cause contraction of extracellular fluid volume and a consequent increase in aldosterone secretion and decrease in GFR; the latter conditions promote sodium conservation by the kidneys. There are probably still other adaptive mechanisms that operate to limit the effectiveness of exogenous steroids in inducing aberrations in electrolyte metabolism.

Structure-Function Relationships of Synthetic Anti-Inflammatory Steroids

Seemingly minor alterations in the chemical structures of steroids often result in very great changes in the biological activity of these compounds. For example, the 11β-hydroxy steroid hydrocortisone is well known for its effectiveness in influencing a large number of biological processes, whereas its 11α-hydroxy stereoisomer 11-epihydrocortisone is practically devoid of biological activity. Steroid chemists in recent years have demonstrated great skill in the development of novel steroids, many of which have exhibited intriguing biological properties. In order to evaluate the specific functional role of a particular substituent of the steroid molecule, one might assay the biological activities of a whole series of compounds possessing the substituent, using as standards for comparison the series of compounds that differs solely in its lack of the substituent in question. Several such studies have been performed in this laboratory. Assays of the acute effects of steroids upon Na^+ and K^+ excretion have been accomplished in adrenalectomized dogs by a method originally developed for the assay of aldosterone.[13] Pertinent results are summarized in TABLE 2. The metabolic effects of steroids in human subjects were studied by methods described elsewhere.[23, 24]

Effects of 9α-halogenation.[25-27] A large number of corticosteroids has been halogenated in 9-position. In every case known to the author the introduction of halogen atoms in 9-position of the corticosteroid nucleus has been found to bring about a general enhancement of biological potency. In most cases the enhancement of electrolyte-regulating potency has been especially pronounced.

Because of their effectiveness in promoting Na^+ conservation, 9α-fluorohydrocortisone and 9α-fluoroprednisolone have found a place as substitutes for aldosterone in the treatment of Addison's disease.[28, 29] Dosage must usually be limited to less than 0.25 mg. daily; use of higher dosages for a period of weeks commonly has led to the appearance of hypertension and hypokalemia. Although these compounds are very potent in suppressing ACTH, experience in the treatment of virilizing congenital adrenal hyperplasia[29] has indicated that the minimal doses required for adequate ACTH suppression are still so high that with continued use they frequently lead to hypertention.

TABLE 2

APPROXIMATE RELATIVE POTENCIES OF SEVERAL ANTI-INFLAMMATORY STEROIDS*

Steroid	Sodium		Potassium	
	Effect	Potency	Effect	Potency
DOC	Retention	1.0	Loss	1.0
Aldosterone	Retention	39	Loss	29
Hydrocortisone	Loss		Loss	0.04
9α-Fluorohydrocortisone	Variable		Loss	5.5
Δ^1-Hydrocortisone (prednisolone)	Loss		Loss	0.03
2α-Methylhydrocortisone	Variable		Loss	1.0
6α-Methylhydrocortisone	Loss		Loss	0.08
6α-Methylprednisolone	Loss		Loss	0.02
9α-Fluoroprednisolone	Variable		Loss	8.0
Triamcinolone	Loss		Loss	0.3
Dexamethasone	Loss		Loss	0.5

* Compared with DOC and aldosterone, assayed for acute effects on Na^+ and K^+ excretion in adrenalectomized dogs.

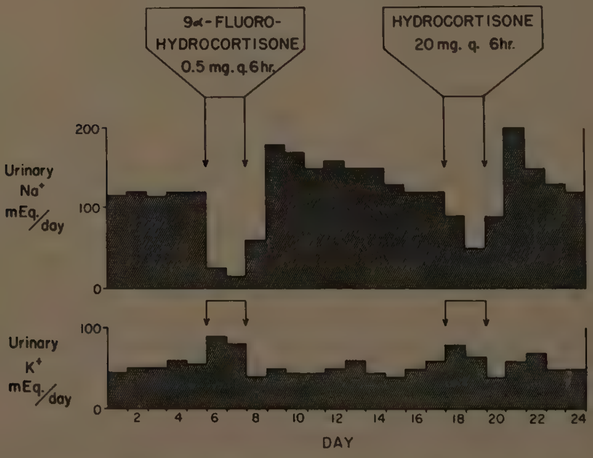

FIGURE 4. Comparison of the effects of hydrocortisone and of 9α-fluorohydrocortisone upon Na^+ and K^+ excretion. The dosage of 9α-fluorohydrocortisone is only one fortieth that of hydrocortisone. Each compound was administered orally. The subject was a normal man maintained on a constant dietary intake.

A representative metabolic study comparing the effects of 9α-fluorohydrocortisone with those of hydrocortisone is illustrated in FIGURE 4.

A paradoxical situation arose in the process of assaying 9α-fluorohydrocortisone in adrenalectomized dogs.[26] Very small dosages of the steroid caused Na^+ retention, but larger dosages caused Na^+ loss (FIGURE 5). The degree of K^+ loss, on the other hand, was a relatively consistent direct function of the dosage of steroid. The explanation offered for the paradoxical effect on Na^+ excretion is that in small dosages the steroid had little effect upon GFR, but did exert an aldosteronelike effect upon the renal tubules, whereas in large dosages the characteristic effect of anti-inflammatory steroids—that of increasing the GFR—more than counterbalanced the aldosteronelike effect. It is possible to simulate this situation by using graded dosages of a combination of an aldosteronelike steroid—for example, desoxycorticosterone (DOC)—and a GFR-raising compound having little or no aldosteronelike activity (for example, prednisone). This is shown in FIGURE 6. In metabolic studies in man the acute GFR effect of 9α-fluorohydrocortisone almost never becomes dominant over the tubular effect, and this compound regularly causes Na^+ retention.

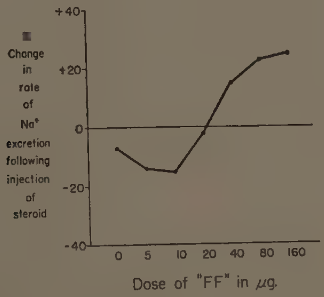

FIGURE 5. Effects upon Na^+ excretion of adrenalectomized dogs of 9α-fluorohydrocortisone, administered intravenously in low and in high dosage. The rate of Na^+ excretion during the hour prior to treatment was taken as the control level. The rate of Na^+ excretion during the interval from 60 to 180 min. after treatment was taken as the response. Responses to each dosage are represented as percentage deviations from the control values. Each point represents the mean of eight 1-dog assays.

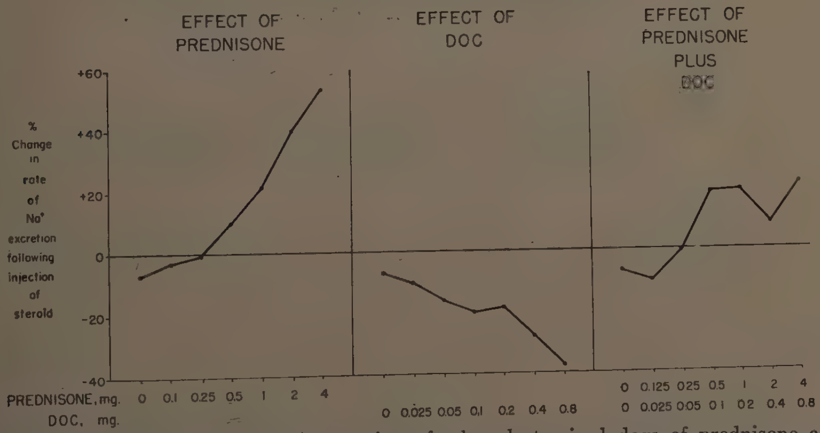

FIGURE 6. Effects on the Na^+ excretion of adrenalectomized dogs of prednisone and desoxycorticosterone, administered intravenously in graded dosages, separately and in combination. The method of charting responses is the same as that described in FIGURE 5. Each point represents the mean of six 1-dog assays.

Effects of 1,2-dehydrogenation. In our laboratory the electrolyte-regulating effects of more than a dozen 1,2-dehydrogenated corticosteroid derivatives have been compared with those of their 1,2-saturated analogues. In most instances the 1,2-dehydrogenated (Δ^1) compounds were slightly less effective than their respective analogues; the changes were never great, however. The most remarkable consequence of 1,2-dehydrogenation is that of a three- to five-fold enhancement of anti-inflammatory potency. Many of these compounds tend to increase GFR, which, insofar as net Na^+ excretion is concerned, tends to counterbalance what little aldosteronelike activity remains. In the adrenalectomized dog Δ^1-hydrocortisone (prednisolone) regularly induces an acute increase in Na^+ excretion. Pechet and Bartter[30] have shown that prednisolone may induce an increase in GFR and a slight Na^+ diuresis in man. Thorn *et al.*[31] have pointed out that with large dosages of prednisolone in man the aldosteronelike action may predominate, resulting in a net retention of Na^+. The practical value of the Δ^1 corticosteroids resides in the fact that their enhanced anti-inflammatory potency enables the therapist to keep dosage at levels that only very rarely are attended by significant Na^+ retention and K^+ loss.[32] FIGURE 7 illustrates a metabolic study in which comparable anti-inflammatory dosages of prednisolone and hydrocortisone were administered to a normal subject and demonstrates clearly the practical advantage of the Δ^1 compound.

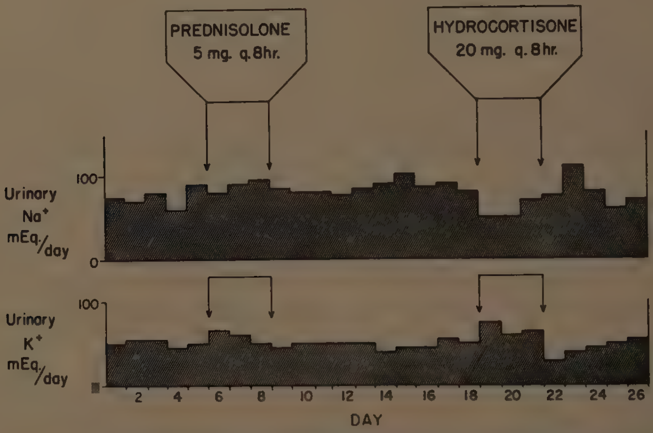

FIGURE 7. Comparison of the effects of hydrocortisone and of prednisolone upon Na^+ and K^+ excretion. The dosage of prednisolone is only one quarter that of hydrocortisone and was adjusted in this manner to demonstrate the relative electrolyte-regulating effects of equivalent anti-inflammatory dosages. Each compound was administered orally. The subject was a normal woman maintained on a constant dietary intake.

Effects of 2α-methylation.[23, 33] The electrolyte-regulating effects of ten 2-methylated compounds have been compared in our laboratory with their respective nonmethylated analogues. Although 2α-methylation altered only slightly the anti-inflammatory and related activities of various corticosteroids, it resulted in very great enhancement of electrolyte-regulating activity of the 11β-hydroxy-corticosteroids. Renal function studies in adrenalectomized dogs indicated that these potent compounds exerted aldosteronelike activity upon the renal tubular exchange of Na^+ and K^+ and had no acute effect upon GFR.

The practical use of this series of compounds has been limited to those conditions in which Na^+ retention is desirable.

Effects of 6α-methylation.[24, 34-36] Eight corticosteroids that bear a 6α-methyl substituent have been studied. In certain steroids (for example, Δ^1-9α-fluoro-21-desoxyhydrocortisone), 6α-methylation attenuates the electrolyte-regulating activity while enhancing the anti-inflammatory activity. The biological consequences of 6α-methylation are so inconsistent from one steroid to another, however, that generalization perilous. The most widely used 6α-methyl steroid, methylprednisolone, is slightly less potent than prednisolone itself in electrolyte-regulating activity. Like prednisolone, methylprednisolone increases GFR and induces loss of Na^+ in acute studies in adrenalectomized dogs. Like prednisolone, it is therapeutically effective as an anti-inflammatory agent in dosages that are practically devoid of aldosteronelike activity.

Effects of 16α-hydroxylation. Dramatic attenuation of electrolyte-regulating activity results from the introduction of an hydroxyl group in 16α position. In 1954, Hirschmann *et al.*[37] reported that 16α-hydroxy-DOC was practically devoid of Na^+-retaining activity. In 1956, Bernstein[38] demonstrated that 9α-fluoroprednisolone could be converted into a compound having negligible aldosteronelike activity by introduction of an hydroxyl group in 16α position. Although a two- to tenfold diminution in anti-inflammatory activity resulted from the introduction of the 16α-hydroxyl group, this compound (triamcinolone) has been widely accepted as a therapeutic agent, in part because it is almost totally devoid of Na^+-retaining activity.[39] Triamcinolone in ordinary anti-inflammatory dosages often induces slight Na^+ loss; presumably, the principal mechanism is that of an increase in GFR. Pechet *et al.*[40] have referred to metabolic studies in which triamcinolone induced potassium excretion out of proportion to losses of nitrogen; this potassium wasting was accompanied by muscular weakness, but not by hypokalemia.

A large number of steroids has been hydroxylated in 16α position by Bernstein and, in every case, the Na^+-retaining activity of the 16α-hydroxyl derivative was markedly reduced relative to that of the original compound.

Effects of 16α-methylation. In our laboratory, 4 steroids bearing 16α-methyl groups have been compared with their respective nonmethylated analogues. The published findings of Arth *et al.*[41] and of Bunim *et al.*[42] were confirmed in that the 16α-methyl derivatives were found to be decidedly less effective than their nonmethylated analogues with respect to aldosteronelike activity. Unlike 16α-hydroxylation, the introduction of a 16α-methyl group was found to enhance slightly the anti-inflammatory potency of each of the corticosteroids studied. The most widely used member of this new series of compounds, and the most potent from the standpoint of anti-inflammatory activity, is 16α-methyl-9α-fluoroprednisolone (dexamethasone). In adrenalectomized dogs, dexamethasone causes an acute increase in Na^+ and K^+ excretion. In endocrinologically normal human subjects, dexamethasone in dosages up to 3 mg./day was found to induce a slight increase in excretion of both Na^+ and K^+. A study comparing the effects of prednisolone, 9α-fluoroprednisolone, and dexamethasone upon Na^+ and K^+ excretion is depicted in FIGURE 8. These findings are in agreement with those of Arth *et al.* and Bunim *et al.* However, it has been the experience of others that mild edema may occur in 10 to 15 per cent of patients receiving dexamethasone as treatment for rheumatoid arthritis[43] or other collagen diseases.[44] Pooling of information from additional investigators will probably be necessary before an exact picture can be composed of the frequency with which aberrations in electrolyte metabolism occur as complications of dexamethasone therapy.

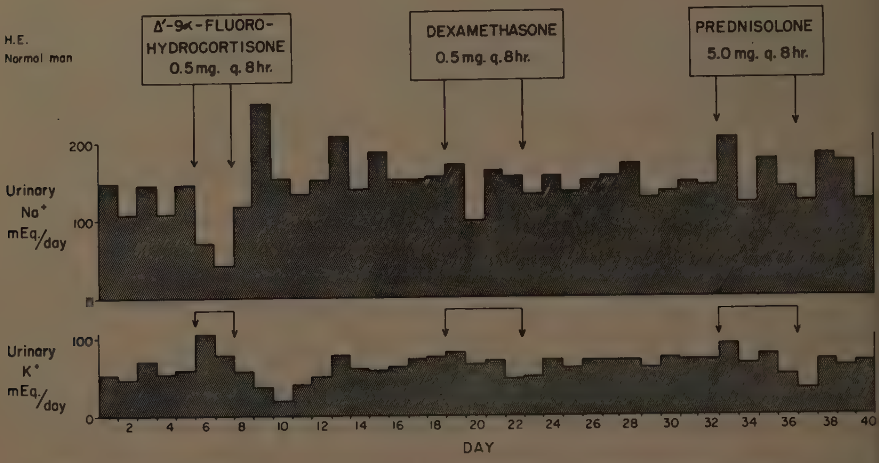

FIGURE 8. The effects upon Na^+ and K^+ excretion of dexamethasone compared with those of its "16-nor" analogue 9α-fluoroprednisolone and those of prednisolone. In dosages shown, these compounds would be roughly equivalent in anti-inflammatory activity, although obviously not equivalent in electrolyte-regulating activity. The dosage of prednisolone is 10 times that of the other compounds. Each compound was administered orally.

Summary

There is no necessary correlation between the anti-inflammatory activity and the electrolyte-regulating activity of steroids. Steroids may induce Na^+ retention and K^+ loss by promoting the renal tubular cation-exchange process through which Na^+ is reabsorbed from K^+, and H^+ secreted into the tubular urine. Steroids may induce Na^+ loss by (1) inhibiting the action of aldosterone upon the renal tubules, (2) increasing glomerular filtration rate, or (3) correcting a pathological stimulus to hypersecretion of aldosterone. Studies of structure-function relationships of the synthetic anti-inflammatory steroids have indicated that, in general, the tendency of corticosteroids to promote Na^+ retention and K^+ loss is greatly enhanced by introduction of a halogen atom into 9α position of the corticosteroid nucleus, slightly decreased by 1,2-dehydrogenation, and greatly diminished by introduction of a hydroxyl or a methyl group in 16α position. The most potent of the currently available anti-inflammatory steroids, dexamethasone, occasionally causes mild disturbances in electrolyte metabolism.

Acknowledgments

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Discussion

Comment: In connection with metabolic effects, may I comment briefly on the action of dexamethasone on calcium, which seems to be so different from that of the above-mentioned adrenocorticosteroids. It has been widely assumed that these steroids have a strongly calcium-losing effect. This is based largely upon the occurrence of the undesirable clinical side effect of vertebral compression fractures, and has derived a little support from some brief measurements of the urinary excretion of calcium following administration of these various steroids.

However, examination of studies of this factor by complete balance observation (the measurement of both urinary and fecal excretion of calcium during considerable periods of 30 days or more) shows that in only one instance has there been the definite observation of over-all calcium loss with steroids such as hydrocortisone, prednisolone, and 9α-fluorohydrocortisone. There have now been 12 to 15 such complete balance studies, about half of them published. I should add that when some increase in urinary calcium was found during such studies, there seemed to be a slight concurrent decrease in fecal calcium so that, over-all, the result was no net change in calcium balance.

With dexamethasone, however, in 2 patients studied at a dosage level of 6 mg./day for as long as 24 days, we noted a definite increase in both urinary and fecal calcium excretion, indicating a definite tendency to calcium loss.

I feel that this point is interesting, since dexamethasone is the first steroid that has given really definite results with respect to calcium.

EFFECTS OF ANTI-INFLAMMATORY STEROIDS ON CARBOHYDRATE METABOLISM, WITH EMPHASIS ON HYPOGLYCEMIC AND DIABETIC STATES*

Thomas F. Frawley, Hansjörg Kistler,† Thomas Shelley‡
Subdepartment of Endocrinology and Metabolism, Albany Medical College, Albany, N. Y.

Ever since the early observations by Bierry and Malloiezel[1] in 1908 that hypoglycemia developed in adrenalectomized dogs, it has become increasingly evident that the adrenal glands are intimately concerned with carbohydrate metabolism. In 1932 Britton and Silvette[2] emphasized the importance of the adrenal cortex in carbohydrate metabolism and the exclusion of this action from its electrolyte-controlling activities. In 1940 the classic studies of Long *et al.*[3] brought to light the effects of adrenalectomy on the level of blood glucose, the increase in liver glycogen after adrenocortical-extract administration in these adrenalectomized animals, and the exacerbation of glucosuria by adrenal extract and crystalline steroids in the partially pancreatectomized animal. In 1940 Thorn and his co-workers[4] published the first of their series of papers dealing with their observations on the intermediary metabolism of patients with Addison's disease. Using crystalline steroids and adrenocortical extract, they showed that some of the clinical and metabolic features of Addison's disease were due to a defect or defects in carbohydrate metabolism, secondary to the lack of a particular type of steroid hormone. Subsequently, these steroids were designated as glucocorticoids, since their main effects appeared to be on some aspect of carbohydrate metabolism. Between 1940 and 1948 numerous workers including, in particular, Thorn, Forsham, and Conn, utilized various preparations of crystalline steroids in man and showed that adrenal-like steroids could be subdivided into those that had mainly carbohydrate effects and those that had mainly electrolyte effects. Cortisone, corticosterone, and 11-dehydrocorticosterone were shown to possess definite but different degrees of glucocorticoid activity. These and all other steroids with definite glucocorticoid activity have an oxygen atom at the 11 position on the steroid molecule. The most marked glucocorticoid activity is seen in those compounds possessing a combination of oxygen atoms at the 11 and the 17 positions on the steroid molecule; those with an oxygen atom at the 17 position alone possess little or no glucocorticoid activity. Verzar,[5] however, seriously questions the advisability of establishing such a classification of steroids, that is, "mineralocorticoids" or "glucocorticoids," since his investigations have shown that all the adrenal steroids have qualitatively the same activities.

With the production of cortisone in increased quantities, and the observations by Kendall and Hench of its anti-inflammatory activity, attention naturally turned to ascertaining the chemical properties required if steroids are to show anti-inflammatory properties. The first obvious parallel observed and emphasized was that between their carbohydrate-regulating activities and their

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† Sterling-Winthrop Research Fellow.

‡ John A. Hartford Foundation Fellow.

anti-inflammatory potencies. With the production of new adrenal steroid analogues, however, it has become increasingly clear that a wide disparity may exist between these two actions and their pituitary suppressive effects.

Methods of Evaluating Carbohydrate Activity of Steroids

The new adrenal steroid analogues have placed a premium on accurate methods for obtaining adequate and reproducible biological assays of their activity. While the present methods used in animals are quite helpful and reproducible, the results obtained and conclusions reached do not necessarily apply to man. The greater part of this problem is our inability to reproduce the animal bioassay test in man, thereby making it impossible to obtain direct comparisons between the effects in animals and in man. The liver glycogen assay in adrenalectomized rats or mice serves as a very useful index of carbohydrate activity. It is not practical to measure liver glycogen deposition in man. Also, there are not enough adrenal-insufficient humans to serve as assay subjects for every new steroid preparation that becomes available. The complexity of the problem may be seen from TABLE 1. Only those metabolic effects believed to be influenced by steroids having glucocorticoid activity are included. Specific carbohydrate effects are listed separately from nonspecific carbohydrate effects. Even though the correlation between the animal assay and the human assay of steroid potency may be highest when a nonspecific measurement is used in a human, it must be emphasized that these effects are not known to be the result of any effect on carbohydrate metabolism.

TABLE 1

PARAMETERS OF CARBOHYDRATE-REGULATING ACTIVITY OF STEROIDS

Animals	Humans
Carbohydrate effects	
Liver glycogen deposition Gluconeogenesis Anti-insulin action Muscle-work test Resistance to stress Hyperglycemic action Diabetogenicity	Hyperglycemia Glycosuria Antihypoglycemic
Non-specific glucocorticoid effects	
Excretion of water load Growth test Lymph node and thymus involution	Pituitary suppression Eosinopenia and lymphocytopenia Uric acid excretion increase Anti-inflammatory Correct abnormal EEG of Addison's disease Increased resistance to stress Excretion of water load Reduced pigmentation in Addison's disease Potassium depletion

Of the specific methods used in animal assay, the liver glycogen assay in adrenalectomized rats or mice is the most useful and serves generally as the standard procedure for comparison of all new as well as old steroid preparations. The muscle-work test of Ingle[6] is equally accurate, but much less simple to perform. The Everse-de Fremery test has fallen into disuse, since it has been shown that the effects measured are determined by the blood volume and electrolyte status of the animal as much as by the presumed carbohydrate effect.[7] For example, desoxycorticosterone, a strong electrolyte-regulating, but extremely weak carbohydrate-influencing steroid, gives a good response with this latter test technique.

In man, for some time, the eosinopenic-inducing property of glucocorticoids was considered to be the best assay method. Some investigators still hold this method in high regard. Some of the difficulties in using eosinophils as an index of adrenocortical function were pointed out in a previous publication.[8]

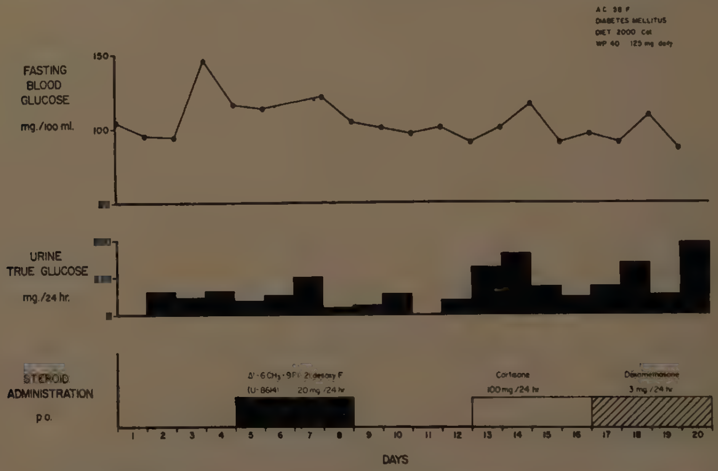

FIGURE 1. The glycosuric potencies of 3 steroids compared in a patient with diabetes mellitus receiving a constant diet and 125 mg. of metahexamide daily. Cortisone and dexamethasone were comparable in a dosage ratio of 33:1.

Recently Thorn and his associates[9] have shown that even the strong electrolyte-regulating steroid, aldosterone, causes an eosinopenic response. Of the specific methods, the induction of glycosuria in the Addisonian patient has much to commend it as an assay procedure.[10] The fact that there is no interference from endogenous glucocorticoids makes this type of assay determination particularly meaningful. This is, however, not a technique likely to be generally available because of limitation of suitable assay subject material. We have been interested in obtaining a solution to this problem of glucocorticoid assay by measuring, in diabetes mellitus patients, the glycosuric response to various steroid preparations. This provides twofold information since, in addition to the glycosuric effect of the steroid, there is an anti-insulin effect measured in terms of an increased blood sugar and an increased insulin requirement. The effects of different steroids in a diabetic subject are shown in FIGURE 1. Cortisone given orally in a dosage of 100 mg./day produced a marked increase in glycosuria. Compared with 3 mg./day of dexamethasone, the degree of glycosuria was essentially the same. This indicated relative potencies of 33:1 (cortisone:dexamethasone) or 27:1 (hydrocortisone:dexamethasone). This ratio is almost twice that obtained in animal bioassays of dexamethasone (17 × hydrocortisone) and corresponds to that obtained by West with his technique of hyperglycemic response in man (TABLE 2). This carbohydrate-potency figure for dexamethasone also agrees closely with that obtained in other studies described below.

TABLE 2

CHEMICAL MODIFICATIONS OF HYDROCORTISONES AND THEIR CARBOHYDRATE ACTIVITY

Chemical modification	Synthetic compounds	Proprietary or common names	Biological half time* for humans (minutes)	Carbohydrate potency (Compound F = 1)	
				Animals† (× Compound F)	Humans‡ (× Compound F)
	Hydrocortisone (Compound F)		95–120	1	1
I. Dehydrogenation					
(a) C_1–C_2	Δ^1-Hydrocortisone	Prednisolone	177–200	3–5	4
II. Halogenation					
(a) C_6	6-Fluorohydrocortisone			11	
(b) C_9	9-Fluorohydrocortisone	Florinef		12.6	6–12
III. Methylation					
(a) C_2	2-Methylhydrocortisone		180	10	
(b) C_6	6-Methylhydrocortisone			4	
(c) C_{16}	16-Methylhydrocortisone			3	
IV. Hydroxylation					
(a) C_{16}					
V. Deoxygenation					
(a) C_{21}					
VI. Combinations					
Ia, IIa	Δ^1-6-Fluorohydrocortisone			81	12
Ia, IIb	Δ^1-9-Fluorohydrocortisone			42	25
Ia, IIIa	Δ^1-2-Methylhydrocortisone				
Ia, IIIb	Δ^1-6-Methylhydrocortisone	Medrol	188	10–16	5
IIb, IIIa	2-Methyl-9-fluorohydrocortisone			30–40	
IIb, IVa	9-Fluoro-16-hydroxyhydrocortisone			4–8	
Ia, IIb, IIIb	Δ^1-9-Fluoro-6-methylhydrocortisone			126	8
Ia, IIb, IIIc	Δ^1-9-Fluoro-16-methylhydrocortisone	Dexamethasone	170–210	17	30–35
Ia, IIb, IVa	Δ^1-9-Fluoro-16-hydroxyhydrocortisone	Triamcinolone		36	5
IIb, IIIb, Va	9-Fluoro-6-methyl-21-desoxyhydrocortisone			23	2
Ia, IIb, IIIb, Va	Δ^1-9-Fluoro-6-methyl-21-desoxyhydrocortisone	U-8614		0.25	2

* Data from Brown *et al.*,[11] Bunim *et al.*,[12] Jenkins and Schemmel,[13] and Dulin *et al.*[14]

† Data from Bernstein *et al.*,[15] Bunim *et al.*,[12] Byrnes *et al.*,[16] Dulin *et al.*,[17] Lyster *et al.*,[18] and Fried and Borman.[19]

‡ Data from West.[20, 21]

Until we find a more precise bioassay for carbohydrate activity in man, considerable discrepancy between animal and human data will prevail. It is sufficient to say that it is not yet possible to predict, from results obtained in animals, the carbohydrate activity of steroids in man. No technique has been found that will replace the need for assaying each steroid individually in man before drawing conclusions as to its carbohydrate activity.

Structure-Function Relationship with Regard to Glucocorticoid Activity

Modifications in the structure of hydrocortisone, the major glucocorticoid of the adrenal cortex, produce marked alterations in its biological activity. To date the following modifications have been made either singly or in combination: (1) dehydrogenation, (2) halogenation, (3) methylation, (4) hydroxylation, and (5) deoxygenation. The glucocorticoid potencies of some representative compounds are listed in TABLE 2. The potencies listed are based solely on a definite carbohydrate effect of the individual steroid without relation to any of its anti-inflammatory, eosinopenic-inducing, or pituitary-suppressing qualities.

It is evident from TABLE 2 that a marked difference often exists between the carbohydrate activity of a steroid in animals and its similar activity in man; this disparity and its implications have already been discussed. It is obviously difficult to anticipate the carbohydrate activity of a new steroid in man from data obtained in animals. With some steroids the correlation between animal and man is good (as with 9-fluorohydrocortisone), while with Δ^1-9-fluoro-16-hydroxyhydrocortisone, for example, the potencies differ widely. Consequently, a continuing need exists for better methods of measuring carbohydrate activity in man.

Glucocorticoids and Hypoglycemia

Steroids such as hydrocortisone and corticosterone have been shown to have a definite glucose effect in man. In previous studies[22] it was shown that intravenous hydrocortisone markedly ameliorated the hypoglycemic symptoms of Addison's disease. Of particular interest was the observation that this effect occurred without a concomitant marked change in blood sugar, and it was suggested that this might be related to an alteration in the transfer of glucose across the cell membrane (particularly in the brain) since the clinical manifestations of hypoglycemia responded so promptly; other mechanisms also may be involved.

In an attempt to heighten the effect of glucocorticoids in hypoglycemia, a patient with Addison's disease, in hypoglycemic adrenal crisis and without electrolyte alterations, was treated with 100 mg. only of intravenous hydrocortisone (FIGURE 2). There was little or no increase in blood sugar, but a definite gradual return of the sensorium developed during a span of 2 hours. Even after this time had elapsed, the blood sugar was still approximately 20 mg./100 ml. With the administration of glucose there was a complete restoration to normal mental and physical activity. We continue to feel that glucocorticoids favorably influence the hypoglycemic state of adrenal insufficiency without significantly altering the blood sugar; another example of this antihypoglycemic effect is shown in FIGURE 3.

Steroid metabolism in hypoglycemia. Although little is known about the fate of secreted hydrocortisone, studies undertaken by Peterson[23] indicate that the main step in the degradation of hydrocortisone is hydrogenation followed by conjugation with glucuronic acid. This degradation of hydrocortisone takes place mainly in the liver, and various factors are involved in the process. However, in a normal individual the degradation of hydrocortisone follows a constant pattern, as measured by the disappearance of intravenously administered labeled and unlabeled cortisol. Peterson found that in certain pathological states such as liver disease the removal of free plasma hydrocortisone is slower than in normal humans, whereas in hyperthyroidism the disappearance of hydrocortisone is accelerated. This suggests that the enzyme systems in-

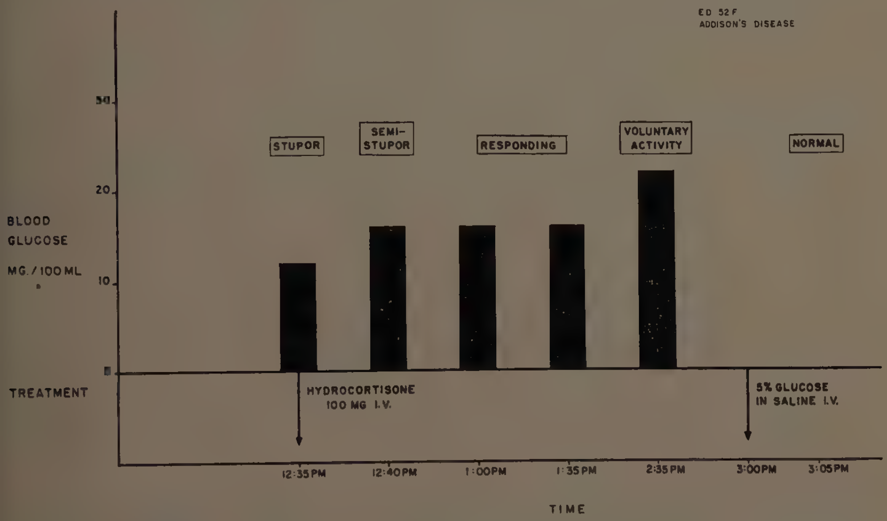

FIGURE 2. Effect of intravenous hydrocortisone in acute adrenal crisis. The clinical manifestations of hypoglycemia were improved without a significant increase in blood sugar.

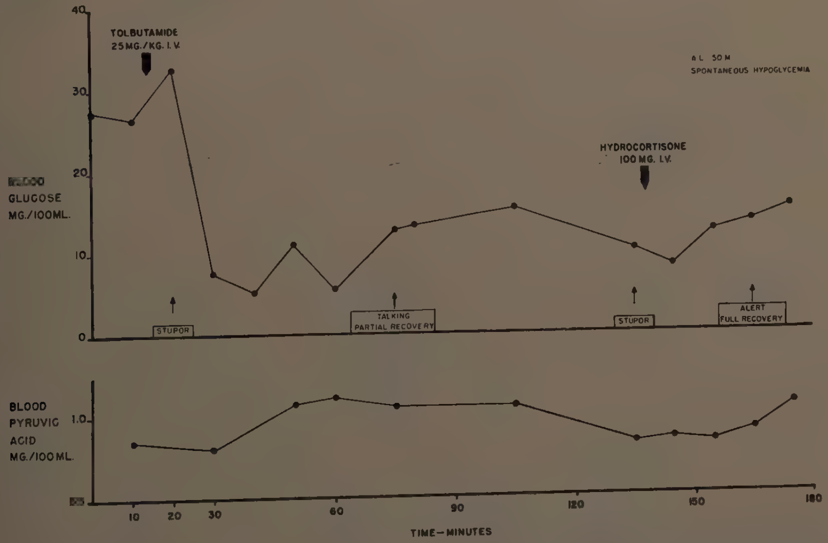

FIGURE 3. Effect of 100 mg. of hydrocortisone (intravenous) in a patient with an islet-cell adenoma during a tolbutamide-induced hypoglycemic episode. There was complete clinical recovery following intravenous hydrocortisone, but the same blood glucose levels had been associated previously with partial recovery only.

volved in the metabolism of hydrocortisone are activated or impaired, depending on the metabolic state.

It was of considerable interest, therefore, to obtain studies on the disappearance of hydrocortisone in a disturbed metabolic state such as hypoglycemia. Although adrenal functions in patients with hypoglycemia have been found repeatedly to be within normal limits, it is conceivable that, because of the hypoglycemic state, there may be an immediate increased need for glucocorticoids and, although these may be secreted in increased amounts, they may be metabolized differently.

In a 50-year-old patient suffering from hypoglycemic attacks for 15 years, the diagnosis of hyperinsulinism was established by the demonstration of Whipple's triad, by preventing hypoglycemia with adrenal steroids, and by the surgical removal of a pea-sized pancreatic adenoma. During an episode of hypoglycemia, easily reproduced by an overnight fast, the patient received 100 mg. of hydrocortisone (133.7 mg. of hydrocortisone hemisuccinate) intravenously within 10 min. Determinations of free plasma hydrocortisone[24] were done 10, 40, 70, and 100 min. after the infusion of hydrocortisone. As shown in FIGURE 4, hydrocortisone disappeared very rapidly from the blood, the half time being 42 min. Also presented are the hydrocortisone disappearance curves and rates in a normal individual who had a half time for hydrocortisone of 108 min. and those of 2 patients with myxedema, who had half times of 145 and 220 min. Increased disappearance rates have been observed in hyperthyroidism.[11, 23] The unexpected finding that during hypoglycemia free cortisol is removed from the plasma 2½ times as fast as in the normal individual deserves further elucidation, especially as all the factors involved in the degradation of steroids are not yet known.

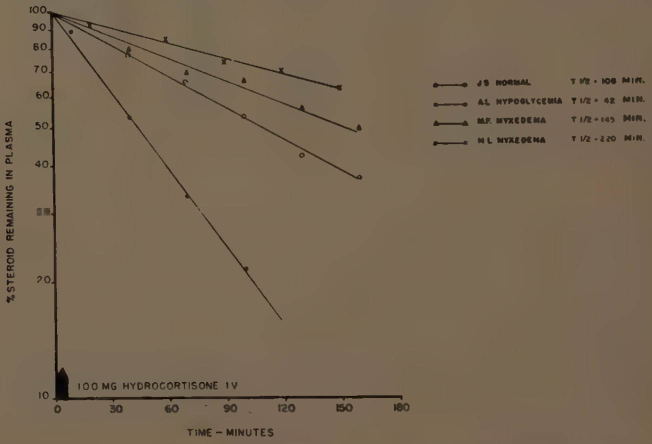

FIGURE 4. Disappearance of free plasma hydrocortisone following a rapid intravenous injection of 100 mg. of hydrocortisone. The biological half times are shown in minutes. The rapid disappearance rate in the hypoglycemic subject A.L. exceeds that observed in hyperthyroidism.[23]

It seems reasonable to theorize that this hypoglycemia had an effect on hepatic enzyme activity that produced more rapid hydrogenation or conjugation of hydrocortisone. Unfortunately, no studies could be performed on the mechanism of conjugation involved. It is conceivable that the increased degradation of plasma hydrocortisone results in an increased turnover and production of adrenal hormones. The fact that normal values were found for conventionally determined urinary 17-hydroxycorticosteroids and 17-ketosteroids suggests that hydrocortisone might be metabolized differently and excreted as other metabolites. Hyperresponsiveness to intravenous ACTH would be expected in such a patient and, in fact, was demonstrated in this patient.

Tomkins[25] has shown that corticosteroid degradation by the liver is in the form of a saturation of the 4,5 double bond of the A ring and is accomplished through 2 separate enzymatic steps. Both steps are dependent on reduced triphosphopyridine nucleotide (TPNH), and Tomkins demonstrated that, under conditions where TPNH production is deranged, the rate of steroid inactivation may be increased (as with thyroxine administration). We suggest that this TPNH alteration may occur in hypoglycemia as the result of enhanced glucose-6-phosphate oxidation. This may explain in part the increased disappearance rate of the infused hydrocortisone in the patient with an insulin adenoma.

Another question concerning this disturbing finding of a rapid disappearance of hydrocortisone during hypoglycemia was whether it might be explained on the basis of an increased production of epinephrine, secondary to the hypoglycemia. Sandberg and his associates have reported that epinephrine does not modify the rate of disappearance of cortisone.[26] With our technique we have determined also the effect of epinephrine on the disappearance rate of intravenous hydrocortisone. In normal subjects, the biological half time of hydrocortisone obtained during an epinephrine infusion (10 μg./min.) was 72 min. With this method, epinephrine did increase the disappearance rate of hydrocortisone, but not to the degree observed during hypoglycemia.

Antihypoglycemic effects of glucocorticoids. Hypoglycemia in individuals suffering from Addison's disease or pituitary insufficiency is relieved promptly with glucocorticoids. Hypoglycemosis occurring in infants and hypoglycemia caused by excessive amounts of insulin (due to either islet cell hyperplasia, adenoma, or carcinoma) is reversed strikingly with glucocorticoids.

Hydrocortisone is more effective than corticosterone in offsetting hypoglycemia. In studies to determine this, a patient with an insulin-secreting tumor served as an experimental subject for comparative evaluations of the antihypoglycemic activity of different steroids.[22] Recently, in another subject with an insulin adenoma of the pancreas, several steroid preparations were given to determine their antihypoglycemic potency. The patient was fasted overnight and usually presented fasting blood sugars of between 30 and 50 mg./100 ml.; the test steroid was then administered intravenously for a 10-min. period, and fasting blood sugars were determined every hour for 3 to 4 hours.

The percentage fall of the blood sugar beyond the initial fasting blood sugar level for each experiment is presented in FIGURE 5. A comparison was made of 100 mg. of hydrocortisone, 20 mg. of prednisolone, 20 mg. of methylprednisolone, and 2 mg. of dexamethasone given intravenously on separate days.

Fasting alone produced repeatedly a 70 per cent fall in blood sugar but, following prednisolone administration, the patient maintained his initial fasting blood glucose level. With dexamethasone the maximum fall was only 18 per cent, whereas with hydrocortisone the blood sugar fell by 25 per cent. Methylprednisolone had the least effect—a 60 per cent fall. Obvious clinical symptoms such as sweating, confusion, stupor, and tachycardia were observed only when the patient underwent a prolonged fast without any steroids.

From the results of this study it would appear that intravenous dexamethasone is superior to intravenous hydrocortisone in preventing hypoglycemia, but that neither substance is as potent as prednisolone. The lack of a substantial effect with methylprednisolone was unexpected. Some of these differences may be explainable on the basis of the biological half times of these steroids (TABLE 2). Those with the lowest biological half times appear to be the most effective with respect to antihypoglycemic potency. More detailed studies using insulin administration combined with steroids are required before absolute conclusions can be drawn regarding a particular steroid. Although the hypoglycemia in the subject studied was regularly reproducible, it is possible that there was considerable daily variation in insulin secretion by the tumor with consequent variation in the apparent antihypoglycemic effect of a given steroid. It is to be noted that the antihypoglycemic potency of dexamethasone (35 to 50 × hydrocortisone) in this patient is of the same order of magnitude as the potency obtained using the glycosuria-inducing method discussed above, and also the same as the potency figure obtained by West,[21] utilizing his technique (TABLE 2).

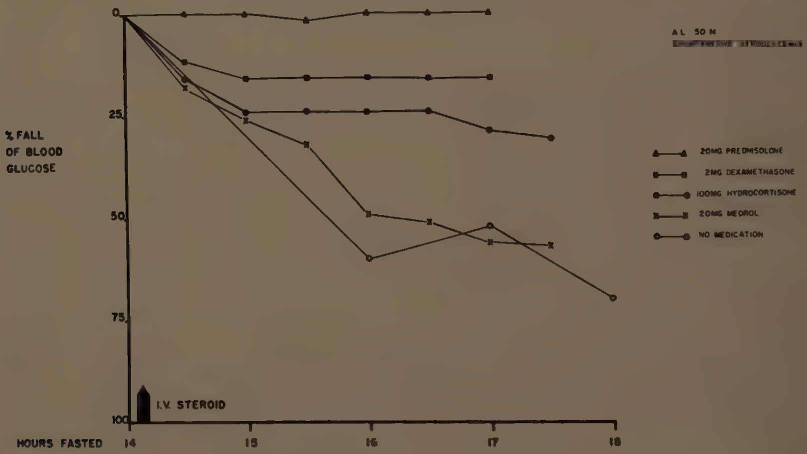

FIGURE 5. Effect of intravenous steroids on hypoglycemia. Separate injections of 100 mg. of hydrocortisone, 20 mg. of prednisolone, 20 mg. of 6-methylprednisolone, and 2 mg. of dexamethasone were compared in this fasted subject who had an islet-cell adenoma. The percentage fall of blood glucose from the initial fasting level is shown for 5 different experiments.

Bunim and his co-workers[12] performed glucose tolerance tests in 3 patients who had received no steroids prior to dexamethasone and found no impairment of glucose tolerance. However, 4 of 5 patients who had received prednisone prior to dexamethasone showed a diabetic response. The investigators are careful to point out that these results are based on "a small group of patients and short term administration of dexamethasone." While our studies of the carbohydrate potency of dexamethasone indicate that it may be stronger than originally thought, they do not necessarily mean that an increased incidence of carbohydrate disturbances is likely to result. The insulin reserve of the majority of patients receiving steroids is such that the development of impaired carbohydrate tolerance is infrequent.[27]

Glucocorticoids and Diabetic States

There is an increasing interest in determining the role of the glucocorticoids in the development of hyperglycemia in various diabetic states. With excessive glucocorticoid production, as occurs in Cushing's syndrome, a diabetic state may result as manifested by hyperglycemia, glycosuria, and a reduced tolerance to a glucose load. Glycosuria itself does not necessarily indicate that a true diabetic state exists, as cortisone will cause glycosuria, although the precise mechanism causing this is in dispute.[28, 29] A normal glucocorticoid production may be responsible in part for maintaining a diabetic state. This is revealed by the lessening of the diabetes of subjects who have undergone hypophysectomy[30] or adrenalectomy,[31] or who have developed anterior pituitary deficiency.[32] In these cases there was a marked reduction in, or discontinuation of their daily insulin requirements. An indirect relationship sometimes exists between some diabetic states and the glucocorticoids. Such may be the case with pheochromocytoma where the diabetic state cannot be explained wholly by the effect of epinephrine on carbohydrate metabolism, but could be accounted for in part by increased glucocorticoid production (reflexly, through epinephrine stimulation of corticotropin production).[33] The development of a diabetic state secondary to glucocorticoid excess is probably related directly to the individual's capacity to increase insulin production and, if this proves inadequate to meet the excessive glucose load, or if beta-cell exhaustion ensues, a diabetic state results.

In 1950 we reported studies of carbohydrate metabolism in patients with Cushing's syndrome, Addison's disease, and Addison's disease coexisting with diabetes.[27] It was noted that normal subjects treated with ACTH for 2 weeks or more infrequently showed evidence of diabetes. A single 25-mg. dose of ACTH given to 5 patients with adrenal hyperplasia resulted in only slight increases in blood sugar, but the same dosage given to 12 diabetic patients produced marked elevations of blood sugar. Cortisone (100 mg.) given to patients with Addison's disease produced slight elevations in blood sugar although, when diabetes coexisted with Addison's disease, one twentieth that amount of cortisone induced marked hyperglycemia and glycosuria. It was concluded that the large functional reserve of the islet tissue in the majority of patients receiving ACTH or steroids protects them from the development of significantly impaired carbohydrate tolerance.[34] If beta-cell exhaustion continues after the removal of the glucocorticoid excess, permanent diabetes ensues, but this is a very rare occurrence. A diabetic state frequently disappears despite continued glucocorticoid excess, and is due to a compensatory increase in insulin production. A diabetic state is sometimes precipitated by some acute disease process and, upon recovery from it, the diabetic state disappears. This is presumably a reflection of the increased glucocorticoid production during the illness. A diabetic state occurring during pregnancy may also be due to increased glucocorticoid production. It has been shown by Cohen *et al.*[35] that the free plasma 17,21-dihydroxysteroids, which include cortisone and hydrocortisone, are elevated during pregnancy. This relationship is not definite, as these steroids may be bound to protein and may not be metabolically active. It has been shown by Bastenie *et al.*[36] that carbohydrate assimilation in normal individuals is impaired initially during cortisone administration, but that in the majority of cases this returns to normal and, in fact, improves beyond the initial control values despite continued cortisone therapy. This latter improvement was paralleled by an increase in plasma hypoglycemic activity (presumably insulin).

Thorn and his co-workers[37] and Ingle[38] suggested in 1950 that it might be profitable to use cortisone or ACTH in the early detection of the reduction of insulin reserves in prediabetic subjects, and Sprague,[39] also in 1950, noting that 2 of 4 patients to whom he administered cortisone developed impaired carbohydrate tolerance, referred to the fact that members of the families of these patients had diabetes. However, it remained for Fajans and Conn[40] to put these observations to a practical use and to show the usefulness of steroids in detecting the prediabetic state in man. These investigators employed the cortisone-glucose tolerance test and found that it separates the nondiabetic relatives of diabetics into groups that differ distinctly from the groups found when the same test is applied to people with no known family history of diabetes.

The diabetic state due to glucocorticoid excess is usually mild and differs from a similar degree of diabetes mellitus in that the former (1) is resistant to insulin; (2) is unlikely to develop ketosis; (3) is a stable form of diabetes readily controllable with insulin, diet, or both; (4) shows evidence of greater protein loss; (5) shows increased liver glycogen deposition; (6) shows other metabolic changes of glucocorticoid excess such as in serum electrolytes and fat distribution; and (7) unlike diabetes mellitus, is reversible. The possible mechanisms by which glucocorticoids produce a diabetic state and the biochemical changes accompanying this state are discussed in greater detail below.

The diabetic state in acromegaly. In acromegaly the incidence of diabetes ranges between 17 per cent[41] and 27 per cent.[42] Some facts concerning this type of diabetes appear quite definite: namely, that diabetes is more frequent in women with acromegaly than in women generally, that insulin resistance is a characteristic, and that the diabetes is usually mild. Less is known regarding the carbohydrate metabolism of acromegaly after the active phase is arrested either by spontaneous arrest, by irradiation of the pituitary, by pituitary suppression hormone treatment, or by hypophysectomy. Darragh and Shaw[43] have reported on the development of diabetes in spite of the apparent arrest of the acromegaly by pituitary irradiation. Almy and Shorr,[44] Balfour and Sprague,[45] and John[46] had acromegalic patients whose diabetes disappeared following the development of pituitary failure. McCullagh[47] has found that the diabetes may be ameliorated by the use of estrogen to suppress anterior pituitary function.

The role of the adrenal cortex in this type of diabetes is not fully known.

Adrenomegaly is often found, and reports of increased urinary 11-oxysteroids have appeared,[48] as well as a few instances of elevated levels of corticotropin.[49] Despite these findings, however, Cushing's syndrome and acromegaly are rarely found to coexist.

Recently we had an opportunity to study the possible role of the adrenal cortex in the carbohydrate tolerance of an acromegalic patient with mild diabetes who was subsequently hypophysectomized. The patient developed a severe postoperative exacerbation of her diabetes mellitus despite the fact that the cortisone replacement of 50 mg./day was well within the commonly accepted daily requirements of hypophysectomized patients. As shown in FIGURE 6, the fasting blood sugar fell promptly to approximately normal levels when cortisone was discontinued while the diet remained constant. FIGURE 7 shows the effect on insulin sensitivity of withdrawing cortisone therapy; steroid withdrawal restored insulin sensitivity. In further studies (FIGURE 8) the blood sugar response to tolbutamide was measured by a technique described previously.[50] On cortisone the hypoglycemic response to tolbutamide was considerably delayed and was similar to that reported previously in diabetes mellitus.[50] Tolbutamide, given after the cortisone was discontinued, resulted in a more prompt but decreased reduction in blood sugar.

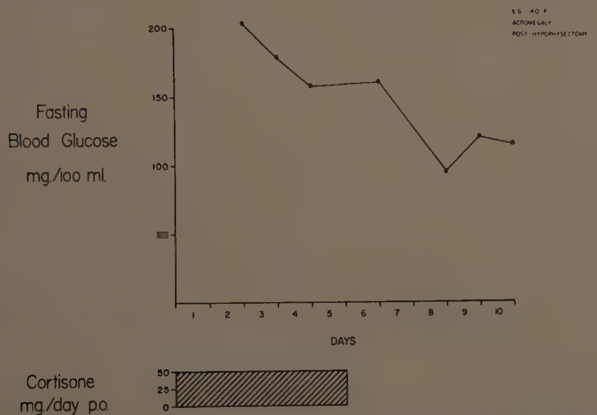

FIGURE 6. Effect of cortisone on blood sugar in a hypophysectomized acromegalic subject. A severe diabetes mellitus developed in this patient who was receiving only 50 mg. of cortisone daily. The discontinuance of the steroid markedly ameliorated the diabetes.

The marked hyperglycemic effects of cortisone in this acromegalic patient were similar to those that have been observed in Addison's disease with coexisting diabetes mellitus.[27] This suggests that the diabetic state of acromegaly may be due, in large part, to increased glucocorticoid production. The degree of disturbed carbohydrate tolerance would then be determined by the degree to which the excess growth hormone stimulates the islets of Langerhans. When this stimulation results in increased insulin production, this counteracts the effect of increased glucocorticoid production. When the growth hormone stimulus is removed, insulin production decreases and, with adrenal hormone activity continuing at a normal or slightly increased rate, a disturbed carbohydrate metabolism results. That the pancreas is able to continue insulin production is evident from the results of the tolbutamide tests. Therefore, although complete beta-cell exhaustion was not present, the stimulation of the beta-cell insulin secretion by growth hormone was lacking because of hypophysectomy. We feel that this evidence suggests that there may be a greater interdependence between growth hormone and the adrenal cortex in the diabetes of acromegaly than may have been appreciated heretofore.

Aggravation of diabetes mellitus. The responsiveness of the individual's com-

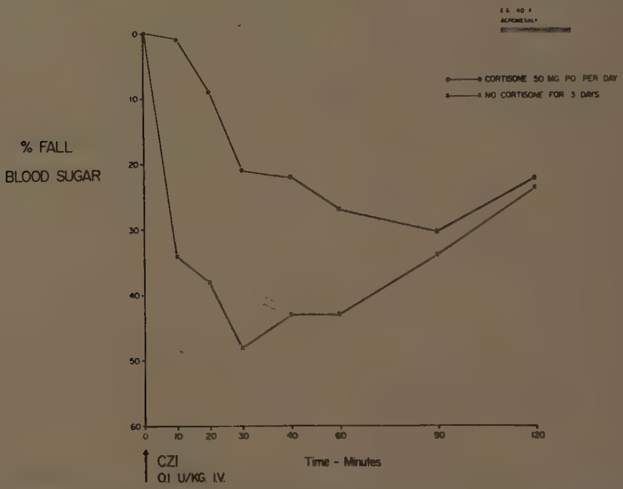

FIGURE 7. Effect of cortisone on insulin response in a recently hypophysectomized acromegalic subject. Insulin sensitivity was restored to normal upon withdrawal of cortisone.

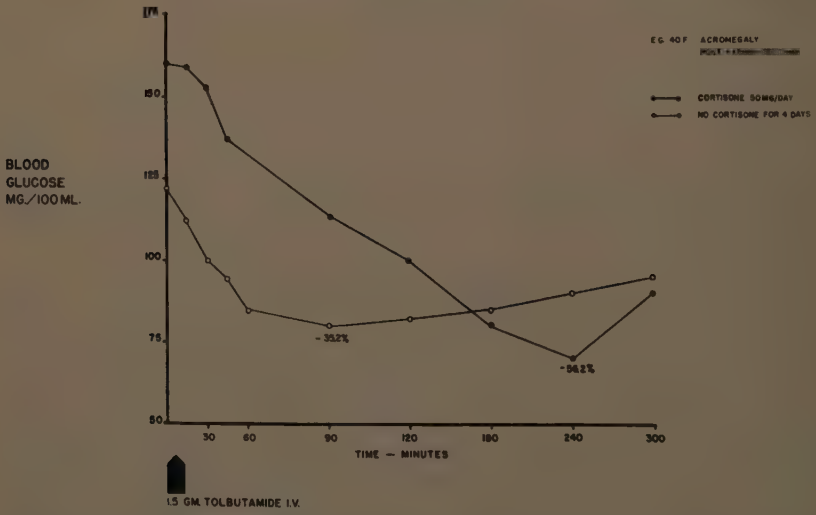

FIGURE 8. Effect of cortisone (50 mg./day, I.V.) on the blood glucose response to 1.5 gm. of tolbutamide, I.V., in a hypophysectomized acromegalic with diabetes. Cortisone caused a delayed diabeteslike response as compared with the normal response following cortisone withdrawal.

pensatory mechanisms governs the degree and direction of the metabolic changes induced by glucocorticoid excess. If insulin production cannot be increased to meet a glucocorticoid-induced hyperglycemia, a diabetic state ensues. With this as a test basis, glucocorticoid administration has been used to reveal a prediabetic state or to confirm the presence of diabetes in an equivocal case.[40] Glucocorticoid excess in diabetes mellitus results in the aggravation of the diabetes and in other metabolic changes. Some of the latter changes may modify the character of the diabetes. Insulin deficiency and glucocorticoid excess produce similar, as well as dissimilar, effects. Some of these main effects are shown in TABLE 3. The cumulative result of insulin lack and glucocorticoid excess is to accentuate the metabolic defects due to insulin lack when these defects are the same; when the effects are dissimilar, the resulting change is that due to insulin lack alone. The whole results in an increased insulin requirement and, if this need is satisfied, the residual metabolic changes are due to glucocorticoid excess alone and consist of decreased proteidogenesis, increased lactate and pyruvate levels, increased liver glycogen deposition, and increased lipogenesis. When the glucocorticoid excess is removed in a controlled diabetic there is an immediate reduction in the demand for insulin, and this may be accentuated if prolonged adrenal cortical excess has resulted in adrenal suppression. In these cases, if the insulin dosage is not reduced at the same time, severe insulin reactions result. When a diabetic has been restabilized following the removal of the glucocorticoid excess, the final insulin dosage may be the same or greater or less than that prior to the glucocorticoid excess; this is due to the many variables involved, such as the improvement of a coincidental disease, beta-cell exhaustion, or inadequate diabetic control during glucocorticoid administration. Although there is no direct correlation between the amount of glucocorticoid excess present and the degree of aggravation of diabetes, in general glucocorticoids in excessive amounts will cause an aggravation of the diabetes. Certain types of "steroid" diabetes may appear to improve during cortisone administration as a result of depression of ACTH by the cortisone and a decreased secretion of the responsible diabetogenic steroid concerned.[51] Diabetes itself is no contraindication to the administration of glucocorticoids, provided there is a sound basis for their use.

TABLE 3

	Insulin lack	Glucocorticoid excess
Carbohydrate	Hyperglycemia	Hyperglycemia
Liver glycogen	Decreased	Increased
Serum lactate and pyruvate	Decreased	Increased
Fat	Decreased lipogenesis	? Unaffected (redistribution of fat storage)
Ketone bodies	Increased	Decreased
Serum cholesterol	Increased	? Unchanged
Protein	Decreased proteidogenesis	Decreased proteidogenesis

Steroid diabetes. The term steroid diabetes was first introduced by Ingle to describe the type of diabetes induced in rats by the administration of Compounds B, E, F, and corticotropin.[52] The ability to produce steroid diabetes in animals varies with the animal species used. Guinea pigs are very susceptible, while rats[53] and cats[54] develop the disorder only under special experimental circumstances.

For reasons not entirely clear, steroid diabetes develops infrequently in man. One suggested cause of this is related to the compensatory increase in insulin secretion by the pancreas;[34] when this is insufficient a diabetic state develops. Even under these circumstances the diabetes is unlike that characteristic of diabetes mellitus. Some of the biochemical differences have been discussed more fully elsewhere;[22] these include insulin insensitivity, hyperpyruvemia, and hypophosphatemia in the presence of steroid excess. It should be added that increased adrenal cortical activity is not characteristic of diabetes mellitus.[27] It was suggested that a compensatory hypoadrenocorticism was present in diabetes mellitus.[34] Detailed studies of adrenal function in diabetics by Rifkin[55] have shown that in the more severe cases of diabetes with degenerative complications there is no evidence of corticoid excess. These studies and others[27, 56] authoritatively and definitely refute the claims of those who persist in suggesting the attractive but unsubstantiated hypothesis that adrenocortical hyperfunction is related to the complications developing in diabetes mellitus.[57]

In a previous paper,[22] particular attention was given to the results of studies made on pyruvic acid metabolism in steroid diabetes. Blood levels of pyruvic acid were elevated consistently in subjects receiving steroids for any significant period of time. It was suggested that this was due to inhibition of pyruvic acid removal rather than overproduction. Disappearance rates of injected sodium pyruvate during a hydrocortisone infusion were reduced,[58] which tends to support the opinion that the glucocorticoids inhibit the mechanisms involved in pyruvic acid removal, as initially presented in 1955.[22] Henneman has corroborated the finding of elevated pyruvic acid levels in the presence of glucocorticoid excess.[59]

Summary

The site of action of the adrenocortical steroids on carbohydrate metabolism and the degree to which they are capable of altering carbohydrate metabolism are gradually becoming clear. Investigations of an increasing number of new adrenal-like steroids have revealed numerous exceptions to the general rules for predicting the potential glucocorticoid activity of a steroid. Many of these new steroids show a lack of correlation between anti-inflammatory activity and glucocorticoid activity. The degree of steroid activity in man has been shown to deviate frequently from that anticipated from animal data. It is necessary, therefore, to evaluate the effects of these steroids in man before conclusions can be made regarding their physiological and pharmacological activities.

Studies of steroid metabolism during hypoglycemia have revealed increased steroid disappearance rates similar to those found in hypermetabolic states such as hyperthyroidism. The administration of adrenal steroids to hypoglycemic patients results in an amelioration of the clinical manifestations prior to the rise in blood sugar. This evidence supports further the hypothesis of a steroid action on either glucose transfer or intracellular metabolism.

Short- or long-term therapy with the adrenal steroids rarely precipitates diabetes mellitus in a patient. This apparently is a result of the considerable insulin reserve possessed by most normal individuals. Steroid-induced diabetes, besides its rarity, is also readily controlled and, therefore, should not be considered as a probable or serious complication of steroid therapy. The biochemical changes accompanying steroid diabetes differ in many respects from those accompanying diabetes mellitus.

It is now definitely known that there is no abnormality of adrenal function in diabetes mellitus. An adrenal mechanism, therefore, is not the cause of the vagaries experienced in diabetic management, nor is an adrenal mechanism the cause of the degenerative complications associated with long-standing diabetes mellitus. Some preliminary studies of the hypoglycemic state and insulin insensitivity seen in acromegaly suggest that in man the adrenal cortex may play a more important role than has been previously appreciated.

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Part III. Clinical Studies

INTRODUCTORY REMARKS TO PART III

Russell L. Cecil
Cornell University Medical College, New York, N. Y.

There have been considerable advances in the field of corticosteroids since the first report by Hench, Kendall, and their able co-workers on the value of these agents in the treatment of arthritis and rheumatic disease. These new advances have had three aspects.

First, there is much broader information regarding the physiological effects of the adrenocortical hormones, especially with respect to metabolism, electrolyte and water balance, capillary permeability, body growth, and hepatic and renal function.

Second, there is a wider application of the corticosteroids in the therapy of both medical and surgical conditions. In the field of medicine proper I may say with feeling that steroid therapy seems to have been tried for almost every group of ailments included in modern medical textbooks. In some cases it has proved to be futile but, on the other hand, many new and important uses for steroids have been discovered. This is well shown by the variety of topics treated in this monograph. It is interesting to note that in most instances the corticosteroids, in contradistinction to other hormones, have their greatest usefulness as an anti-inflammatory rather than as a substitution product.

Third, many new corticosteroids have been isolated. It is in this domain that the pharmaceutical laboratories have made such outstanding contributions. It is a great tribute to medical science in the United States that, in the short space of ten years, such important advances have been made in the isolation and study of new steroids. Most improvements have been made in the area of potency although, of course, various other changes have been produced as well.

The seven most important agents now in actual use are cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, and dexamethasone.

As potency has increased, dosage has decreased from an average of 25 to 50 mg. for cortisone to 0.5 mg. for dexamethasone. Unfortunately, this remarkable progress in potency has not eliminated the occurrence of untoward side effects, and these, of course, present major problems when steroid therapy must be continued for long periods.

THE TREATMENT OF RHEUMATOID ARTHRITIS WITH ADRENOCORTICOSTEROIDS AND THEIR SYNTHETIC ANALOGUES: AN APPRAISAL OF CERTAIN DEVELOPMENTS OF THE PAST DECADE*

Edward W. Boland
Department of Medicine, St. Vincent's Hospital, Los Angeles, Calif.

The era of corticosteroid therapy in rheumatoid arthritis began ten years ago when Hench *et al.*[1, 2] discovered that the administration of cortisone and hydrocortisone rapidly reduced articular inflammation and tended to reverse the abnormal metabolic and biochemical alterations characteristic of the disease. During this period the relation of adrenocorticosteroids and their synthetic analogues to rheumatoid arthritis has been the subject of intensive inquiry, and the attributes and inadequacies of these compounds as treatment agents have become well defined.

The principles, objectives, and schemes for the administration of steroids in rheumatoid arthritis have been determined by, and adapted to, their inherent limitations as treatment agents. The practical application of cortisone and hydrocortisone and their synthetic analogues has been governed by the following considerations.[3, 4]

(1) The benefits are only suppressive, not curative; therefore, if they are to sustain improvement in a chronic disease such as rheumatoid arthritis, they must be administered more or less continuously for an indefinite period.

(2) In addition to the drugs' anti-inflammatory action, they incite manifold physiological responses in various organs and tissues and, frequently, these are objectionable. The occurrence and intensity of unwanted effects depend, in general, on dosage and the length of administration.

(3) Certain pathological states may be aggravated by the hormones and, when these conditions coexist in a patient with rheumatoid arthritis, they serve as relative or absolute contraindications for the use of these agents.

(4) Benefits cannot always be preserved indefinitely because some patients become relatively refractory to the drugs after prolonged administration.

(5) The steroids frequently fail to halt progression of the rheumatic process even while symptomatic relief is being maintained.

(6) Extended use of the drugs produces functional depression of the patient's adrenal cortices and anterior pituitary gland which, though reversible, creates a potential hazard requiring special protective measures during periods of extraordinary stress.

In accord with these considerations, certain policies or "rules" have evolved regarding the indications for, and the employment of, adrenocorticosteroids and their analogues in rheumatoid arthritis. These may be summarized as follows.

(1) Steroids should be reserved for carefully selected cases: those with active and potentially reversible disease.

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(2) More conservative therapy should be given a fair trial first, especially when the disease is mild or of short duration and the process has a good chance for natural reversal.

(3) Steroids should not be prescribed to the exclusion of other measures. A sound comprehensive program should be employed concomitantly; this would consist of well-regulated rest and exercise, properly balanced diet, avoidance of undue emotional stress, physiotherapeutic procedures and graded muscle exercises, careful handling of affected joints with proper supports and splints, occupational and rehabilitative measures, and simple analgesics.

(4) The basic policy should be to promote and uphold that degree of disease suppression that is feasible with dosages that are well tolerated on a long-term treatment basis. In general, complete inhibition of the disease should not be sought—rather, both the patient and the physician must be satisfied with the improvement that may be sustained with "safe" levels of dosage. Dosage must be individualized according to the activity of the disease, the response of the patient, and his susceptibility to adverse reactions.

(5) Satisfactory degrees of improvement cannot be expected for all patients: the dosage requirements for good control are greater than can be tolerated in some cases, especially those with severe or very active disease. Furthermore, adequate control may be lost in other patients because they eventually become resistant to the drugs or because the disease progresses during treatment.

(6) When, for any reason, steroid administration is stopped, treatment must be gradually discontinued or "tapered off"—not suddenly withdrawn.

(7) Under urgent conditions (such as surgery, severe infection, or injury) extra amounts of steroid should be given to cope with the added stress.

CORTISONE AND HYDROCORTISONE: OVER-ALL RESULTS FROM SYSTEMIC THERAPY

The results reported from long-term therapy with cortisone or hydrocortisone show considerable variation. Some investigators have estimated that not more than 25 per cent of rheumatoid patients may be controlled successfully for 2 years or longer, but most have found that adequate improvement may be maintained in one half or more of their patients.[5] The disparity is accounted for, in part, by dissimilarities in the composition of the various series in respect to disease severity, by divergences in schemes of dosage, and by differences in judgment as to the degree of induced hyperadrenal manifestations that can be tolerated safely.

Four years ago the results of hydrocortisone therapy in 150 of our patients with rheumatoid arthritis were analyzed.[6, 7] Maintenance doses of hydrocortisone ranged ordinarily from 50 to 65 mg. in severe cases, from 40 to 50 mg. in moderately severe cases, and from 25 to 40 mg. in moderate cases. The drug was given uninterruptedly, and the maintenance dosage was manipulated from time to time to accommodate shifts in disease activity or to control adverse reactions. Minor endocrine side effects, such as slight-to-moderate facial mooning, hypertrichosis, slight peripheral edema, or irregular glycosuria, were usually looked upon as acceptable annoyances and not as sufficient reasons for stopping treatment. Adjunctive measures such as regulated rest, avoidance of emotional stress, physiotherapy, and a well-balanced diet (relatively low in salt and with caloric restriction, when indicated) were prescribed simultaneously.

At the end of 1 to 3 years of observation, 59 per cent of the patients whose arthritis had not been successfully regulated by measures other than steroid therapy were held in major improvement by hydrocortisone. The benefits were less than satisfactory in the remaining 41 per cent, although many were furnished some measure of helpful relief and improved functional capacity. As might be expected from the foregoing considerations, the over-all results in a group of patients treated for longer periods (a minimum of 3 years) were less impressive; the improvement status was graded as adequate or major in 53 per cent of the patients and inadequate in 47 per cent (FIGURE 1). The most frequent reason for inferior results was the intrusion of objectionable hormonal side reactions, prohibiting the use of fully effective doses; hence, the failure to achieve or maintain adequate control of rheumatic manifestations in nearly one half the patients while adhering to dosages considered safe for prolonged administration.

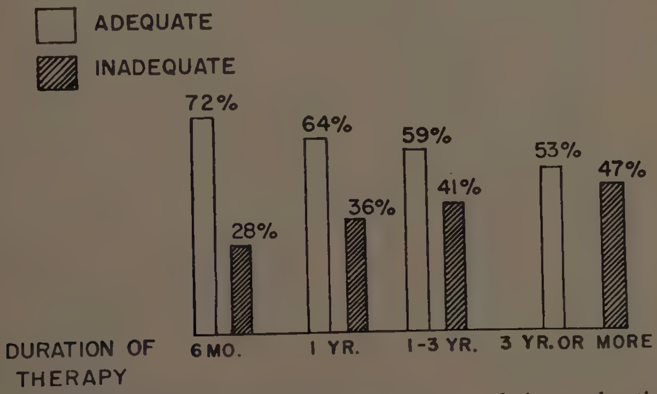


FIGURE 1. Over-all results of hydrocortisone therapy in relation to duration of treatment on 150 patients with rheumatoid arthritis.

CHEMICALLY MODIFIED CORTICOSTEROID COMPOUNDS

Chemists have worked diligently during the past 5 years to devise synthetic steroid compounds that could be applied more successfully than hydrocortisone and cortisone as treatment agents; steroids that, ideally, would retain powerful anti-inflammatory action, but would be free of those physiological properties that induce objectionable effects. Hope that compounds with enhanced therapeutic efficiency might be designed stemmed from knowledge that, by substituting certain chemical groupings and by making minor configurational changes in the molecular structures of hydrocortisone and cortisone, it was possible to alter their biological properties quantitatively and sometimes selectively. Considerable progress has been made in the synthesis of steroid analogues, and this has proceeded in step-by-step fashion, with information derived from the study of one derivative leading to the preparation of still another. Actually, hundreds of modified compounds have now been prepared; many have been investigated clinically, many more have been tested in animals, and a few have been introduced commercially as suppressive drugs for rheumatoid arthritis and other responsive conditions. Chemical alterations of cortisone or hydrocortisone that have yielded substances of therapeutic interest include the insertion of a halogen atom at C-9, a double bond in the A ring, a methyl radical at the C-6 position, a hydroxyl group at C-16, and a methyl group in the alpha or beta configuration at C-16. Singly or in combination, these changes have produced substances with different physiological characteristics.

Fludrocortisone (9α-Fluorohydrocortisone)

The first important discovery in the evolution of chemically modified compounds was made by Fried and Sabo[8, 9] in 1953 when they demonstrated that the anti-inflammatory potencies of hydrocortisone and cortisone could be enhanced and that other biological effects could be altered by inserting halogen atoms at the ninth carbon position. A number of 9-halogenated compounds was produced and, depending on whether a chlorine, fluorine, iodine, or bromine atom was substituted, these exhibited variances in glucocorticoid and mineralocorticoid activities. The 9α-fluoro derivative of hydrocortisone (fludrocortisone) was particularly interesting; in animals it was decidedly more powerful in glycogenic activity, in causing thymus involution, and in retaining sodium.[10, 11] The compound was found to possess antirheumatic potency that, on a milligram-for-milligram basis, was 10 times greater than its precursor.[12, 13] However, its sodium-retaining and potassium-losing properties were multiplied to an even greater extent (approximately 125 times) and, although doses as small as 3 or 4 mg./day suppressed rheumatoid manifestations, they caused severe edema. The compound's excessive electrolyte activity precluded its systemic application as an anti-inflammatory drug, but its modified properties demonstrated clearly that the anti-rheumatic effects and other actions of hydrocortisone could be altered quantitatively by changes in its formula.

Prednisone and Prednisolone (Δ^1-Cortisone and Δ^1-Hydrocortisone)

The introduction of a double bond between the first and second carbon atoms in the steroid ring was a second major innovation. This was accomplished by Herzog and his co-workers[14] in 1954 and resulted in the production of prednisone and prednisolone, the Δ^1 analogues of cortisone and hydrocortisone, respectively. The adrenocortical activity of these compounds, as measured by eosinopenic response, liver glycogen deposition, and thymus involution in adrenalectomized mice, was shown to be 3 to 4 times greater than for the parent hormones. Clinical studies demonstrated that their antiphlogistic power, per milligram, was much greater than that of the natural hormones, yet their electrolyte activity was not increased. These observations provided additional evidence that steroids with augmented anti-inflammatory activity could be prepared synthetically and that the potentiation need not be accompanied by proportional increases in all of the other physiological effects.

During the past 4 years prednisone and prednisolone have been widely employed in the treatment of rheumatoid arthritis, and most investigators have found them preferable to cortisone and hydrocortisone as antirheumatic agents.

Certain general observations drawn from clinical experiences may be summarized.[15-18]

(1) The antirheumatic potencies of prednisone and prednisolone, per milligram, average about 4 times that of hydrocortisone, but the potency ratios are not constant in individual cases; in 1 series they ranged from 2.4:1 to 5.3:1 (average, 3.97:1).[18] The dosages required are considerably smaller than for hydrocortisone, and the usual range is about 12.5 to 17.5 mg./day for severe cases, 10 to 12.5 mg. for moderately severe cases, and 5 to 10 mg. for moderate cases.

(2) Prednisone and prednisolone are, for practical purposes, equally potent and interchangeable.

(3) The patterns of initial and subsequent improvement from the analogues are much the same as from cortisone and hydrocortisone when dosages of comparable antirheumatic strength are employed. From the standpoint of over-all statistical results, there seems to be little preference among prednisone, prednisolone, and hydrocortisone for initial steroid treatment in suitable candidates.

(4) Prednisone and prednisolone are capable of improving the conditions of some patients who have lost satisfactory rheumatic control after protracted hydrocortisone or cortisone therapy. In one series nearly one half of the patients, whose improvement had deteriorated with hydrocortisone, regained major improvement after prednisone or prednisolone therapy was substituted.[19] In many instances (but not all) the achievement of better rheumatic control could be attributed to the elimination of salt and water retention, which permitted the use of more effective doses.

(5) The over-all incidence of adverse reactions is as great with prednisone and prednisolone as with hydrocortisone when these are administered in dosages of equal antirheumatic strength, but the compounds differ in proclivity to induce certain side effects. Salt and water retention and a tendency toward blood pressure elevation are negligible with prednisone and prednisolone; conversely, these analogues are more prone to promote such unwanted reactions as digestive complaints, peptic ulcers, vasomotor symptoms, and cutaneous ecchymoses. Other effects such as facial mooning, fat pads, nervous symptoms, hypertrichosis, acne, skin tags, and disturbance of glucose tolerance appear with similar frequency when comparable antirheumatic doses of the Δ^1 derivatives and hydrocortisone are given.

9α-Fluoroprednisolone (Δ^1*-9α-Fluorohydrocortisone*)

It was logical for chemists to prepare a steroid that contained both a double bond between carbon atoms 1 and 2 (as in prednisolone) and a fluorine atom at the ninth carbon position (as in 9α-fluorohydrocortisone). The compound that resulted—9α-fluoroprednisolone—could not be applied therapeutically, but it proved to be interesting from the standpoint of subsequent chemical permutations. The antirheumatic potency of 9α-fluoroprednisolone in rheumatoid patients was estimated to be 15 times greater than that of hydrocortisone; however, the substance promoted severe and intolerable sodium retention and potassium loss, which prohibited its systemic use as an anti-inflammatory and antiallergic agent.[20]

Triamcinolone (16α-Hydroxy-9α-Fluoroprednisolone)

The next important step in the synthesis of "tailored" steroids was made by Bernstein and his co-workers[21] in 1956, when a hydroxyl grouping was placed at the 16-carbon position. The addition of this substituent was found to abolish the sodium-retaining properties of 9α-fluoro compounds. Although 9α-fluoroprednisolone could not be applied clinically because of its excessive electrolyte metabolism, triamcinolone, which differs chemically only by the presence of a hydroxyl radical at C-16, has been used extensively during the past 2 years. Experience has not established that the drug has a higher therapeutic index than prednisone and prednisolone. Because it is virtually free of sodium-retaining activity, triamcinolone may perhaps be employed more successfully in the occasional patient who develops edema from prednisone and prednisolone. However, triamcinolone produces unique reactions of its own in some patients, and these have served as deterrents to its general application. The peculiar effects include anorexia, weight loss, muscle weakness, nausea, and other vague gastrointestinal symptoms, plus dizziness, fatigue, cutaneous erythema, and a "general toxic feeling." The antirheumatic strength of the compound is slightly greater than that of prednisolone (on the average, about 10 per cent greater)[22] and, aside from sodium retention, its adverse reactions (including peptic ulcers, osteoporosis, and aggravation of diabetes) are much the same as those of other Δ^1 steroids.

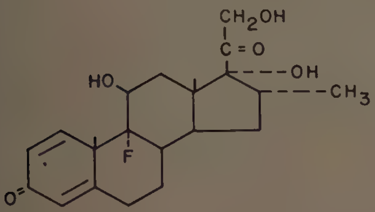
Methylprednisolone (6α-Methylprednisolone)

In 1955 and 1956 a series of methylated corticosteroid analogues was synthesized by Hogg and his collaborators.[23, 24] Biological experiments in animals established the fact that, when a methyl radical was substituted for a hydrogen atom at the C-2 position, selective enhancement of electrolyte metabolism occurred. If the methyl grouping was introduced at the C-6 position instead, the resulting compound did not exhibit increased sodium retention or potassium loss. Preliminary studies in animals of 1 of the compounds—6α-methylprednisolone—suggested that it might possess a useful quantitative dissociation of properties: sodium retention was not observed at any dose level tested, glycogen deposition activity was found to be 10 times greater than that of hydrocortisone, and anti-inflammatory strength (gauged by granuloma inhibition) was 6 times greater than that of hydrocortisone.[25, 26]

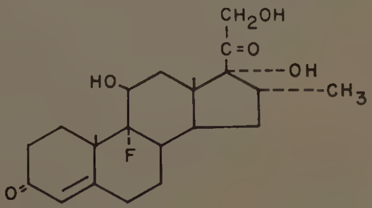
Metabolic studies in human subjects, however, revealed the fact that the effects of 6α-methylprednisolone do not differ from those of prednisolone itself, except that its sodium-retaining and potassium-losing activities may be less.[27-29] Clinical observations in patients with rheumatoid arthritis have indicated that the anti-inflammatory and associated metabolic effects of prednisolone are not substantially altered by the substitution of a methyl radical at the sixth carbon position. From the standpoint of practical therapeutic application, 6α-methylprednisolone has proved to be a satisfactory antirheumatic agent but, when compared to prednisolone, it has not exhibited clearly defined advantages or disadvantages. The 2 steroids promote similar initial response in previously untreated patients, uphold clinical improvement equally well on long-term administration, and, insofar as can be determined, provoke adverse effects that, for the most part, are similar in kind, degree, and incidence.[27, 30-32] Comparisons of milligram potency have disclosed the fact that the antirheumatic strength of 6α-methylprednisolone is somewhat greater (15 to 25 per cent) than that of prednisolone.[27, 31]

16-Methyl Derivatives of Hydrocortisone and Cortisone

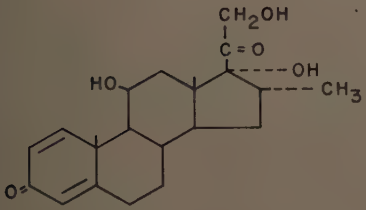
The latest achievement in the evolution of steroid analogues is that of Sarett and his collaborators who in 1957 synthesized a new family of compounds containing, in common, a methyl grouping at the C-16 position.[33] Screening tests in animals for determining the biological behavior of these derivatives, accomplished by Silber and his group,[34] indicated that methylation at the sixteenth carbon position promoted striking changes in several physiological properties, including a decided intensification of anti-inflammatory action and an absence of sodium retention with the experimental doses used. The relative potencies of several biological activities of four 6-methyl derivatives in the hydrocortisone series (16α-methyl-9α-fluoroprednisolone, dexamethasone; 16α-methyl-9α-fluorohydrocortisone; 16α-methylprednisolone; and 16α-methylhydrocortisone; all shown in FIGURE 2) and two 16-methyl derivatives in the cortisone series (16α-methylprednisone and 16β-methylprednisone) are listed in TABLE 1. Each of the compounds displayed varying degrees of greater physiological potency than hydrocortisone and, in the case of 16α-methyl-9α-fluoroprednisolone



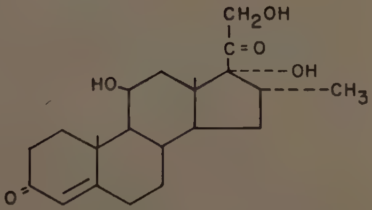
16 α- METHYL, 9 α FLUORO-
PREDNISOLONE



16 α - METHYL, 9 α FLUORO-
HYDROCORTISONE



16 α METHYL PREDNISOLONE



16 α METHYL HYDROCORTISONE

FIGURE 2.

particularly, certain properties were tremendously enhanced by methylation at the sixteenth position. Of interest and importance was the finding that the anti-inflammatory potency of dexamethasone, as gauged by granuloma inhibition, was augmented to a much greater extent than glycogen deposition (190 times as compared with 17 times), suggesting that there might be a therapeutically useful dissociation of these 2 effects. Of considerable significance also was the finding that the placement of a methyl substituent at the beta position in 16β-methylprednisone diminished the glycogenic, but not the anti-inflammatory activity of the parent compound.[35]

Table 1

Relative Potencies of Certain Biological Activities of 16-Methyl Corticosteroids as Determined in Animals*

	Thymus involution (potency times hydrocortisone)	Granuloma inhibition (potency times hydrocortisone)	Adrenal atrophy (potency times hydrocortisone)	Glycogen deposition (potency times hydrocortisone)
16α-Methyl-9α-fluoroprednisolone (dexamethasone)	140–200	200	100–175	20
16α-Methyl-9α-fluorohydrocortisone	22	36	28	12
16α-Methylprednisolone	10–15	16	10–18	5
16α-Methylhydrocortisone	1.3–2.4	3	1–3.5	2
16α-Methylprednisone	7–12	12	7	3
16β-Methylprednisone	20	26	18	1

* Adapted from Silber *et al.*,[34] and from Silber, personal communication.

Table 2

16-Methyl Corticosteroids: Antirheumatic Potencies Compared to Prednisolone

Steroid	No. of patients	Dosage ratios: new steroid to prednisolone		Potency ratios: new steroid to prednisolone
		Range	Average	
16α-Methyl-9α-fluoroprednisolone (dexamethasone)	21	1:5 to 1:10	1:7.3	7.3:1
16α-Methyl-9α-fluorohydrocortisone	11	1:2.5 to 1:4.2	1:3.2	3.2:1
16α-Methylprednisolone	7	1:1 to 1:1.7	1:1.3	1.3:1
16α-Methylhydrocortisone	12	1:0.6 to 1:1	1:0.7	0.7:1
16α-Methylprednisone	12	0.75:1 to 1.3:1	1:1.1	1.1:1
16β-Methylprednisone	4	1:1	1:1	1:1

In a recent study the antirheumatic potency of each of the 6 new 16-methylated steroid analogues was compared[36] with that of prednisolone (TABLE 2). This was accomplished by transferring treatment in carefully selected patients back and forth from prednisolone to the test substance, ascertaining the milligram dosages required to maintain equivalent degrees of improvement.

Dosage comparison studies made with dexamethasone showed that the dosage ratios of dexamethasone to prednisolone varied widely in individual patients (from 1:5 to 1:10), but that in the majority the range was from 1:6 to

1:8. In the group of patients tested, the average antirheumatic potency of dexamethasone, per milligram, was about 7 times that of prednisolone, a finding that established the compound as the most powerful antiphlogistic steroid yet synthesized. A similar estimate of its relative antirheumatic potency has been made by others.[37]

Compared with prednisolone, the antirheumatic strength of 16α-methyl-9α-fluorohydrocortisone was found to be approximately 3 times greater, and that of 16α-methylprednisolone about one third greater. Surprisingly, the antirheumatic potency of 16α-methylhydrocortisone was roughly 70 per cent that of prednisolone. The antirheumatic potencies of 16α-methylprednisone and of 16β-methylprednisone were compared with that of prednisolone and, as far as could be determined, the effects of the 3 steroids were found to be about equal; if differences existed, they were too small to calibrate clinically.

Dexamethasone (16α-Methyl-9α-Fluoroprednisolone)

Since December 1957 I have tried to determine the therapeutic efficiency of dexamethasone as compared with that of prednisolone. Ninety-two patients with active rheumatoid arthritis have been treated with the compound and have been observed for periods of from 6 to 9 months. For purposes of analysis the patients were divided into 3 groups: first, those who received dexamethasone as initial steroid treatment (19 patients); second, those whose arthritis was adequately controlled with prednisolone and whose treatment was changed to dexamethasone (28 patients); and third, those who were not controlled adequately with prednisolone and whose treatment was replaced by dexamethasone (45 patients).

Mode of administration. Ordinarily the daily requirement of dexamethasone was divided into 3 or 4 doses ingested following meals and at bedtime with food. This division of dosage was strictly adhered to during the early phases of the investigation so that direct dosage comparisons with prednisolone could be made. Later many of the patients took the total daily requirement in 2 doses, following breakfast and the evening meal; in most instances, antirheumatic control during the 24-hour period was about as satisfactory as when the drug was taken more frequently. Complemental medicaments were withheld during the study except for antacids that eventually were prescribed routinely with each dose of the drug. Initially, no special dietary instructions were given except for patients with gastrointestinal symptoms, roentgenographically demonstrated peptic ulcers, and coexisting diabetes mellitus; later it was necessary to instruct all patients to control their weights carefully and to curtail their caloric intakes in order to prevent excessive gains. Each patient was treated on an ambulatory outpatient basis.

Observations in patients given dexamethasone as initial therapy. For the 19 patients not previously treated with steroids, dexamethasone was prescribed in initial doses that averaged 1.5 mg./day for the group and, according to the severity or activity of the disease, ranged in individual patients from 1.0 to 2.5 mg. Effort was made in each case to establish adequate control of the disease in deliberate fashion with relatively small initial doses, in the hope of avoiding adverse effects from the beginning; ordinarily, the amounts administered initially were only slightly larger than the estimated maintenance dose. Adjustments in dosage were made by small increments and decrements, usually 0.25 mg. at a time.

The pattern of immediate response and subsequent improvement was much the same as with other effective anti-inflammatory steroids prescribed in much larger dosages. After 6 to 9 months of continuous therapy, improvement was gauged as adequate (marked or very marked) in 15 of the 19 patients, or 79 per cent (TABLE 3). The average daily maintenance dose at analysis was 1.13 mg.

TABLE 3

RESPONSE TO DEXAMETHASONE AFTER 6 TO 9 MONTHS OF THERAPY IN 19 PATIENTS NOT PREVIOUSLY TREATED WITH STEROIDS

Case	Sex	Disease severity	Dosage (mg./day)		Improvement			Adverse effects at analysis (Grading: 1 to 4)
			Initial	Maintenance	Degree	Adequate	Inadequate	
1. GS	M	Severe	2.5	1.5	Very marked	X		Prepyloric ulcer (asymptomatic)
2. RY	F	Severe	1.5	1.0	Moderate		X	Mooning (3), fat pads (2), increased weight (3), ecchymoses (1)
3. RM	F	Severe	1.75	2.25	Slight		X	Mooning (3), fat pads (2), bloating (3)
4. CS	F	Severe	1.0	0.75	Very marked	X		
5. RA	M	Moderately severe	1.5	1.5	Marked	X		No aggravation of diabetes
6. FC	M	Moderately severe	2.0	2.5	Marked	X		
7. GC	F	Moderately severe	2.0	0.75	Very marked	X		
8. GG	F	Moderately severe	1.0	0.75	Marked	X		
9. HG	M	Moderately severe	2.0	1.0	Moderate		X	Mooning (1), fat pads (1), increased weight (1), no aggravation of diabetes
10. MJ	F	Moderately severe	1.5	0.75	Very marked	X		Hypertrichosis (1), ecchymoses (2)
11. RM	F	Moderately severe	2.0	2.0	Marked	X		Mooning (2), hypertrichosis (1)
12. PN	F	Moderately severe	2.0	1.5	Moderate		X	Mooning (2), increased weight (2)
13. JP	M	Moderately severe	2.0	0.75	Very marked	X		Prepyloric ulcer (asymptomatic)
14. RB	F	Moderate	1.0	0.5	Very marked	X		
15. IC	F	Moderate	1.0	0.75	Marked	X		Mooning (1), fat pads (1)
16. WC	M	Moderate	1.0	0.75	Marked	X		Very slight aggravation of diabetes
17. SF	F	Moderate	0.75	0.75	Marked	X		
18. MH	F	Moderate	1.0	0.75	Very marked	X		
19. TK	M	Moderate	1.0	1.0	Very marked	X		Ecchymoses (1)
Avg.			1.5	1.13				

and ranged from 0.5 mg. to 2.5 mg. Eleven of the 19 patients, or 58 per cent, developed steroidal side effects (TABLE 3) that were minor and acceptable in 9, but sufficiently pronounced in 2 patients (both with severe disease) to warrant cessation of the drug after 6 (Case 2) and 8 months (Case 3). The over-all results in relation to improvement and side effects did not differ significantly from those obtained from prednisone or prednisolone in a group of similar composition and with similar duration of treatment.[18]

Observations in patients transferred from prednisolone to dexamethasone. That dexamethasone was capable of maintaining satisfactory response among patients amenable to prednisolone therapy was evident in 28 patients whose treatment was changed while they were being maintained successfully on prednisolone. The average daily dosage was 11.25 mg. for prednisolone and 1.35 mg. for dexamethasone. The average dose of dexamethasone was about one eighth that of prednisolone, slightly less than a calculated equipotent dose.

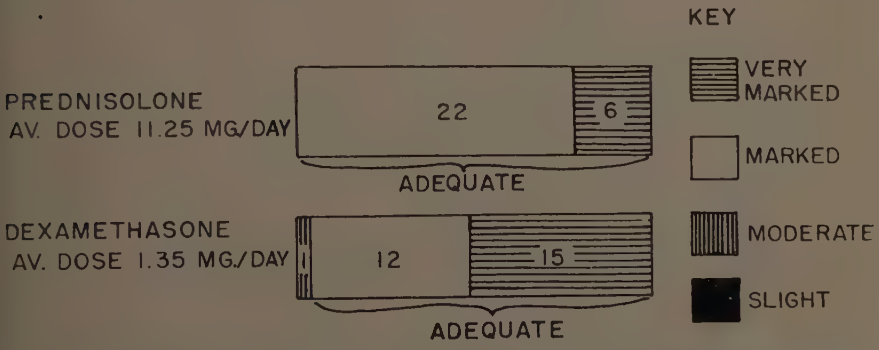


FIGURE 3. Status of improvement 6 to 9 months after transfer to dexamethasone of 28 patients adequately controlled on prednisolone.

Six to 9 months after the change, 27 of the 28 patients had retained adequate rheumatic control, and the degree of improvement had advanced from marked to very marked in 9 patients (FIGURE 3). Because the dosages used for prednisolone and dexamethasone were of comparable antirheumatic strength, comparisons of adverse reactions were of interest. When the additional period of steroid administration (6 to 9 months) was taken into consideration, the total incidence of unwanted reactions from the 2 drugs could be judged as similar but, as discussed below, they differed in their tendency to promote certain individual side effects.

Changes in the improvement status of 45 patients who had been poorly controlled on prednisolone are shown in FIGURE 4. This was a stubborn group of patients, 43 (96 per cent) of whom suffered from severe or moderately severe disease. Most had been on steroid therapy for long periods and had received dosages considered to be maximum with respect to safety. Many had been controlled successfully at one time or another, but with continuation of treatment their conditions had deteriorated to inadequate levels. Attempts were made to achieve better rheumatic control by cautiously increasing the dosages (in terms of antirheumatic potency) of dexamethasone to amounts exceeding those used for prednisolone. The average daily dosage was 10.4 mg. for prednisolone at the time of transfer to dexamethasone, and 1.5 mg. for dexamethasone at analysis. At the end of 6 to 9 months, improvement had been elevated to, and maintained at, adequate levels in approximately one third (17 of 45) of the patients. However, the total number of adverse reactions for the group had increased (149 to 180); disappearances of such side effects as edema, digestive symptoms, and nervous excitation in some patients were more than counterbalanced by excessive weight gain, increased ecchymotic skin lesions, thinning of the skin, facial mooning, abdominal girth, and abdominal bloating and distention in others. In 7 cases undesired effects were sufficiently objectionable to prompt discontinuance of the drug.

Adverse effects from dexamethasone. A number of general observations regarding unwanted side effects from dexamethasone follow:

(1) The over-all incidence of adverse reactions from dexamethasone was about the same as from prednisolone when equally effective antirheumatic doses were given. However, certain differences in individual side effects were noted.

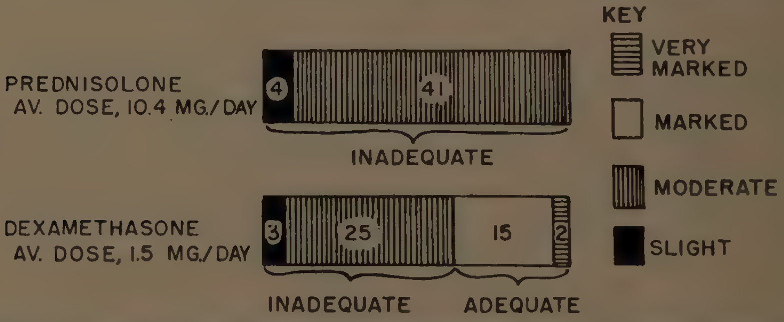


FIGURE 4. Status of improvement 6 to 9 months after transfer to dexamethasone of 45 patients not adequately controlled on prednisolone.

(2) Peculiar symptoms, such as have been noted with triamcinolone (headache, dizziness, fatigue, anorexia, weight loss, muscle weakness, and cutaneous erythema) did not occur during dexamethasone administration.

(3) Peripheral edema developed in 5 of 92 patients (5 per cent). In general, the tendency to salt and water retention was less than with prednisolone and decidedly less than with hydrocortisone.

(4) None of the patients developed hypertension or demonstrated aggravation of pre-existing hypertension.

(5) Dexamethasone appeared to have about the same tendency as prednisolone to provoke facial mooning, supraclavicular fat pads, and hypertrichosis when the drugs were given in doses of corresponding antirheumatic strength.

(6) The rate of occurrence (56 per cent) and the severity of ecchymotic skin lesions with dexamethasone were greater than with prednisolone.

(7) Among the most common side effects encountered, and certainly the ones that were most objectionable to patients, were quickening of appetite (30 per cent of cases), excessive weight gain (23 per cent), and the development of abdominal girth (17 per cent).

(8) Approximately 10 per cent of the patients experienced abdominal distention or bloating. In 2 instances this was so pronounced that treatment was changed to another steroid.

(9) It would appear that dexamethasone may be administered in effective antirheumatic doses to patients with mild or moderate diabetes mellitus without further disrupting carbohydrate metabolism; at least, this was indicated from the experiences of 4 patients with coexisting diabetes. Three were well maintained with doses of 1.75, 1.5, and 1.25 mg./day, respectively, and neither glycosuria nor the requirement for insulin was increased. The fourth patient, whose disease was controlled by dietary restriction alone, noted occasional glycosuria during the administration of dexamethasone in doses of 1.0 mg./day. Previous trials with prednisolone and hydrocortisone had aggravated his diabetic state so greatly that it had been necessary to discontinue the drugs entirely.

(10) Nervous symptoms were rarely encountered (4 per cent) with dexamethasone administered in doses up to 3.0 mg./day. None of the patients experienced mental excitation to a degree that required either cessation of therapy or alteration of dosage.

(11) The incidence of symptoms suggestive of peptic ulcer was low (2 per cent), but the incidence of roentgenographically demonstrable peptic ulcers was considerably higher (8.6 per cent), and as great as we had found with prednisone and prednisolone.[19] Routine upper gastrointestinal X-ray studies were made in 70 patients who had taken dexamethasone for 3 months or longer. Six active peptic ulcers were detected; 5 of these were prepyloric in location. Four were entirely asymptomatic, 1 was mildly symptomatic, and only 1 was accompanied by typical ulcer symptoms. With strict ulcer management, and without discontinuing the drug or reducing its dosage, 5 of the 6 ulcers were shown roentgenographically to have healed within 6 weeks. In the sixth patient a prepyloric ulcer was smaller (on roentgenographic examination) after 6 weeks of treatment, although a new ulcer appeared in the duodenum. Treatment was then changed to prednisolone, and rigid ulcer management was continued but, after another 8 weeks, neither lesion had healed and steroid therapy was subsequently withdrawn. Since it was demonstrated that dexamethasone, like other anti-inflammatory steroids, has ulcerogenic properties, antacids have been prescribed routinely for our patients with each divided dose of the drug.

SUMMARY

The preparation of 16-methylated steroid compounds represents an important step along the path that, it is hoped, will lead eventually to the development of an ideal suppressive agent for rheumatoid arthritis and other responsive diseases. Their discovery has brought investigators closer to unraveling the complex interrelationship that exists between the chemical structure and biological properties of steroids, and perhaps nearer to the preparation of a "tailor-made" derivative whose anti-inflammatory activities are separated completely from the undesirable effects of adrenocortical steroids. Dexamethasone, the latest modified steroid that has been made available therapeutically, is by far the most potent antirheumatic compound that has been synthesized.

It is highly effective in suppressing the manifestations of rheumatoid arthritis and has the capacity, with uninterrupted administration, to maintain improvement in a significant proportion of patients and in some whose control on other steroids has been lost. As a practical therapeutic agent, it now appears that dexamethasone, like certain other available steroids, possesses both advantages and disadvantages. Clinical experience with the compound has not been sufficiently long, however, to warrant a final appraisal of its over-all therapeutic efficiency—that is, its capacity to maintain suppression of disease activity in relation to the avoidance of objectionable side effects.

Acknowledgment

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EXPERIENCE IN GREAT BRITAIN WITH STEROIDS (PARTICULARLY DEXAMETHASONE) IN RHEUMATOID ARTHRITIS*

Oswald Savage
West London Hospital, London, England

The appraisal of ten years' experience with corticosteroids—drugs that are being used in the treatment of so many conditions—is a most important event. In this paper I shall give a summary of our experience with these drugs in Great Britain in the treatment of rheumatoid arthritis.

In 1950, at the instigation of Philip Hench, a small supply of cortisone was made available to us by Merck & Co., Inc., Philadelphia, Pa., and that year we reported the first European trial in rheumatoid arthritis. Although the material was sufficient only for a 10-day comparison with cholesterol in 5 patients, a dramatic effect was demonstrated.[1]

In 1951 supplies of cortisone were distributed to a few centers for continuous administration, and the next year a number of us reported[2] that, of 20 patients who were unable to work because of rheumatoid arthritis, 17 had returned to their occupations while taking the drug.

In 1954 we published a report[3] on 20 patients who had cortisone for 16 months or more and of whom, again, 17 had returned to work. At that time we stated that other methods of treatment such as rest, salicylates, and gold should be tried before steroids were considered, and that remains our policy. The reason for this is that, of several surveys of rheumatic diseases carried out in England recently, one at Leigh,[4] a small Lancashire town, showed that rheumatoid arthritis can be a very mild disease.

We have now studied 112 patients with rheumatoid arthritis on long-term steroid treatment. Eighty females and 32 males have been followed meticulously and have had clinical and pathological assessments each month. A dozen patients have had the drug continuously for more than 6½ years, 82 were started on cortisone, and 30 were started on 1 of the newer analogues.

Of the 20 crippled patients first reported on in 1954 (when 17 had returned to work), a recent 5-year survey showed 10 still at work. Five had died, although in only 1 case (a perforated ulcer) was death associated with steroids. Of the others, 1 died of Parkinson's disease, 2 of cancer, and 1 in an automobile accident. The remaining 5 are comfortable and independent, but unable to work.

Fearnley and his colleagues[5] have reported satisfactory results with a 2-year observation of prednisone in rheumatoid arthritis.

Early experience made it clear to many of us that, with powerful drugs available for the first time, we must find improved methods of measuring rheumatoid arthritis objectively in order to determine when the inflammatory element of the disease was suppressed so that the dose could be lowered to

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* That part of the work reported in this paper that was done at the West London Hospital, London, England, was aided by grants from the Don Mason Research Foundation of the West London Hospital Medical School, and by grants from The Empire Rheumatism Council and the Medical Research Council, both in London, England.

avoid toxic effects. New techniques have become routine, such as measuring finger joints by jewelers' ring sizes[6] and testing the grip with a Beaumanometer.[7] Much work is being done to devise simple objective measurements in this disease.

The main practical benefit of steroids has been to improve function in severe rheumatoid sufferers. Selection of patients for this treatment is carried out in most departments on a purely practical basis; that is, if patients regain independence and return to their occupations through the use of these drugs, the continuous supervision that is necessary for treatment is considered worthwhile. It has been the policy to use steroids as continuous treatment in rheumatoid arthritis, and emphasis has been laid on the careful selection of patients, with contraindications considered to be peptic ulcer, diabetes, psychosis, permanent joint damage, and osteoporosis.

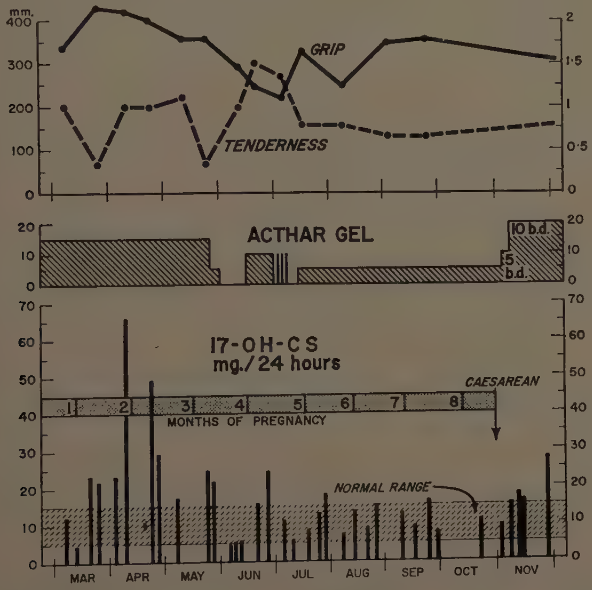

FIGURE 1. Clinical and steroid-output measurements throughout pregnancy. Patient F.B., female, 39 years old.

We have had 4 pregnancies in patients on corticosteroids; in no case have complications arisen, and all the infants have been normal. FIGURE 1 shows the course of rheumatoid arthritis and the steroid output followed throughout pregnancy during long-term treatment with corticotropin. It may be seen that we were able to reduce dosage from 15 to 5 U./day because of the increased steroid output (shown by Richard Bayliss[8] in 1955). When we attempted to withdraw the drug entirely there was a clinical relapse, with a return of tenderness, and declines in grip strength and steroid output.

Emphasis has been laid on side effects in all reports made in England. One author states that the "preoccupation of many observers with these mild side effects reminds one of a house-proud woman overconscious of a speck of dust which the visitor has not noticed."

There is no doubt that to clinicians the bugbears of continued steroid therapy have been peptic ulceration, with the possibility of perforation and hemorrhage, and osteoporosis, which may result in fractures in a normally minor injury. Because of this, the aim throughout has been to keep the maintenance dose as low as possible in the hope of avoiding these severe complications.

Rounding of the face in women has been an almost constant accompaniment of treatment with oral steroids, but it has never been necessary to stop treatment for that reason. Patients accept it and, on occasion, have said they prefer it to their rather haggard appearance before treatment. It is noteworthy that it tends to diminish after several years' administration of steroids.

In our early days with cortisone, edema was quite frequent, although it has never been a serious clinical problem and is even less common now, because of the use of the newer analogues. We eliminate the extra fluid with diuretics such as chlorothiazide.

In 1953 we saw 2 cases of hypokalemic alkalosis due to potassium loss. Both had epigastric discomfort followed by generalized weakness, and both were diagnosed by the low serum-potassium levels and changes in the electrocardiogram. The symptoms disappeared on administration of 8 gm./day of oral potassium. We have seen no symptoms of hypokalemic alkalosis since then, and we no longer give extra potassium or restrict salt intake.

Increased appetite, with resulting obesity, followed by knee and foot strain caused us some difficulty in our early cases. We take rather strong measures to avoid this and now, after an explanation to the patient, threaten to withdraw the steroid if the normal weight is exceeded. We have not yet found it necessary to carry out this threat.

The side effects mentioned above have been strikingly absent in male patients, and none has caused us to withdraw steroids in either sex.

As already mentioned, the complication that has troubled us most in long-term therapy has been peptic ulceration. This is not so much because of its frequency as because perforation and hemorrhage have occurred without warning.

Of our 112 patients, 13 have had peptic ulcers, 3 of which have perforated, resulting in death in 1 case and bleeding in 2. Although there has not been a large number of ulcers, the fact that a few caused medical or surgical emergencies makes us apprehensive when a patient on steroids complains of dyspepsia. On each attendance, patients are asked whether they have indigestion, and if such is reported as either severe or persistent, an X-ray examination of the gastrointestinal tract is carried out. Small ulcers are treated medically without withdrawing the steroid and, as a rule, heal. With persistent ulcers the steroid is withdrawn, but if severe arthritis returns we advise partial gastrectomy and a renewal of corticosteroids. This has been done with success in 4 patients.

Osteoporosis with fracture occurred twice in our series. Of course, this is a side effect we should like to eliminate. In some cases, fractures can be due to early overactivity when rapid suppression is achieved with high doses. We had an experience with this in our first case, that of a woman who had not been outside her home for five years. On the third day with cortisone we encouraged her to walk outside the hospital and she tripped on the curb and broke her nose.

It may seem that the severe side effects reported by us have been rather few. There are two reasons for this: first, that we have had the advantage of reports from researchers in the United States before each steroid became available, and therefore were on guard; and second, that we are able to keep close observation on our patients.

Difficulties occurred with these long-term cases when conditions requiring surgery arose. In the ordinary run of life, with a group of patients who have been restored to independence and are working, some will inevitably meet with accidents and with incidents such as strangulated hernia, appendicitis, and sepsis.

Surgeons in our country were reluctant to operate on patients using steroids because they feared the wounds would not heal. Often, without our knowledge they would stop the drug, not realizing that they were running a real risk of postoperative adrenal crises. It has been an uphill struggle to educate our surgeons in this matter.

It is the anesthetists who have most recently become aware of this problem, and intravenous hydrocortisone is now part of their equipment. From the beginning we have continued the current oral dosage and have added an intramuscular depot of steroid to cover the period of surgical stress.

We have carried out this routine in the thirty operations performed in our series. FIGURE 2 shows these have varied from severe procedures such as cup arthroplasties and a thyroidectomy to minor sepsis. As we have reported,[9] the wounds have healed normally and postoperative complications have been insignificant.

Recently we had the opportunity of carrying out studies on dexamethasone, and the following reports are made on behalf of colleagues in Great Britain. Each of us has carried out a different program, so that a comprehensive, although brief, survey has emerged.

Dudley Hart at the Westminster Hospital, London, England, has compared the suppressive effect of prednisolone and dexamethasone in 25 cases of severe rheumatoid arthritis. Nine were male and 16 female, and their ages varied from 33 to 70; none was in the first year of the disease. The response was measured by means of subjective improvement, the size of the finger joints (according to standard jeweler's ring sizes), tenderness, strength of grip, and the sedimentation rate. All patients (who were both in- and outpatients) had been assessed in this way regularly for some months and were shifted from prednisolone to dexamethasone and back without their knowledge. Two were shifted, tablet for tablet, each from 5 mg. of prednisolone to 0.4 mg. of dexamethasone, with severe and immediate relapse. Six were shifted each from 5 mg. of prednisolone to 2 tablets (0.8 mg.) of dexamethasone and, in the remainder, each 5 mg. of prednisolone was replaced by 1 mg. of dexamethasone (a ratio of 5:1).

Of these 25 patients, 14 preferred dexamethasone and 11 preferred prednisolone; this was supported by the assessments. FIGURE 3 shows the effect during one day on a patient who improved with dexamethasone. Particular notice was taken in these cases of any complaint of indigestion. In 13 there were no such complaints with either drug; in 6 there were equal numbers of complaints with both drugs; in 3 the indigestion was worse with dexamethasone; and in 3 it was worse with prednisolone.

Hart also studied other conditions. In 2 female cases of scleroderma there was no difference between the drugs in 1, and less edema with dexamethasone in the other. In 2 females with disseminated lupus, there was no difference between the drugs, nor was there any in 1 boy, aged 16, with ulcerative colitis.

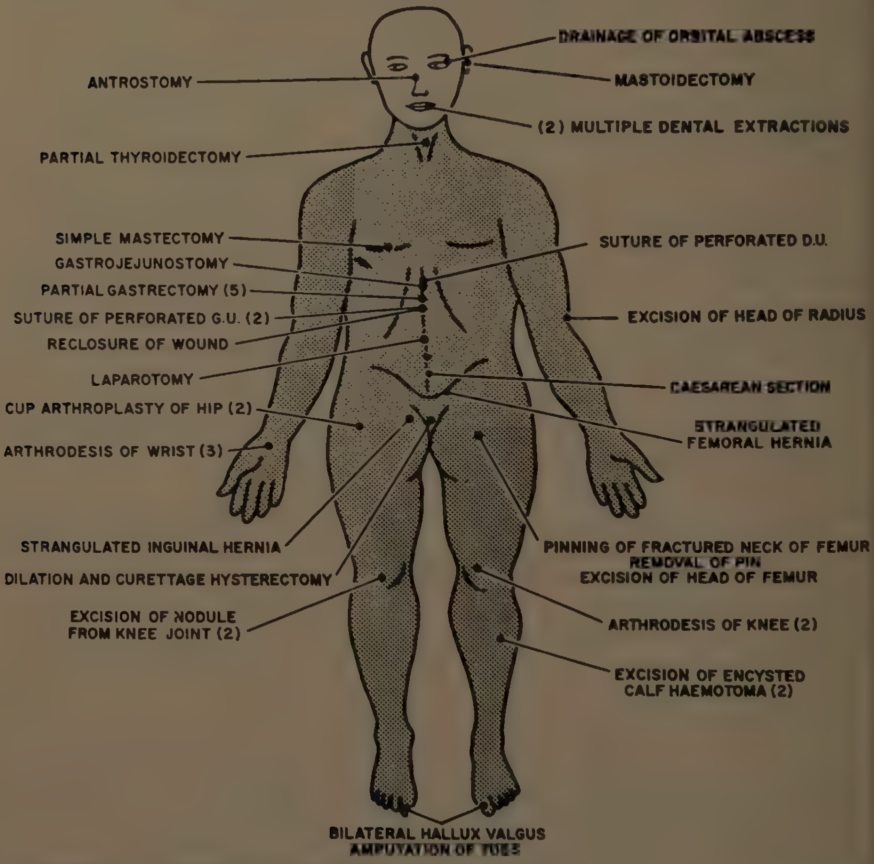
DRAINAGE OF ORBITAL ABSCESS
ANTROSTOMY
MASTOIDECTOMY
(2) MULTIPLE DENTAL EXTRACTIONS
PARTIAL THYROIDECTOMY
SIMPLE MASTECTOMY
SUTURE OF PERFORATED D.U.
GASTROJEJUNOSTOMY
PARTIAL GASTRECTOMY (5)
SUTURE OF PERFORATED G.U. (2)
EXCISION OF HEAD OF RADIUS
RECLOSURE OF WOUND
LAPAROTOMY
CAESAREAN SECTION
CUP ARTHROPLASTY OF HIP (2)
STRANGULATED FEMORAL HERNIA
ARTHRODESIS OF WRIST (3)
STRANGULATED INGUINAL HERNIA
PINNING OF FRACTURED NECK OF FEMUR
REMOVAL OF PIN
EXCISION OF HEAD OF FEMUR
DILATION AND CURETTAGE HYSTERECTOMY
EXCISION OF NODULE FROM KNEE JOINT (2)
ARTHRODESIS OF KNEE (2)
EXCISION OF ENCYSTED CALF HAEMOTOMA (2)
BILATERAL HALLUX VALGUS
AMPUTATION OF TOES

FIGURE 2. Operations performed without complications in a group of 112 patients on long-term steroid treatment.

A case of status asthmaticus in a 27-year-old male was also studied, and no difference was noted.

In none of these miscellaneous cases was there any dyspepsia with either drug, and Hart makes the comment that it always seems to be the rheumatoid patients who get dyspepsia with steroids. I have heard this remark from others in our country.

At the West London Hospital we have concentrated on cases we were unable to control satisfactorily with other steroids, either because of side effects or because of the necessity for a dose that, in our experience, would lead inevitably to trouble if continued for long. All the cases were of severe active rheumatoid arthritis uncontrolled by other methods of treatment, and all were shifted without interruption from another steroid.

In 6 cases the problem was dyspepsia to the extent that we were unable to obtain adequate suppression with prednisolone without observing the appearance of this symptom in a severe form. On shifting to dexamethasone, we obtained adequate suppression in a dose ratio of 1:6 with the prednisteroid. In 3 cases the dyspepsia was abolished, and in 3 it remained. In 3 other cases we had inadequate suppression of the arthritis with 20 mg./day of prednisolone

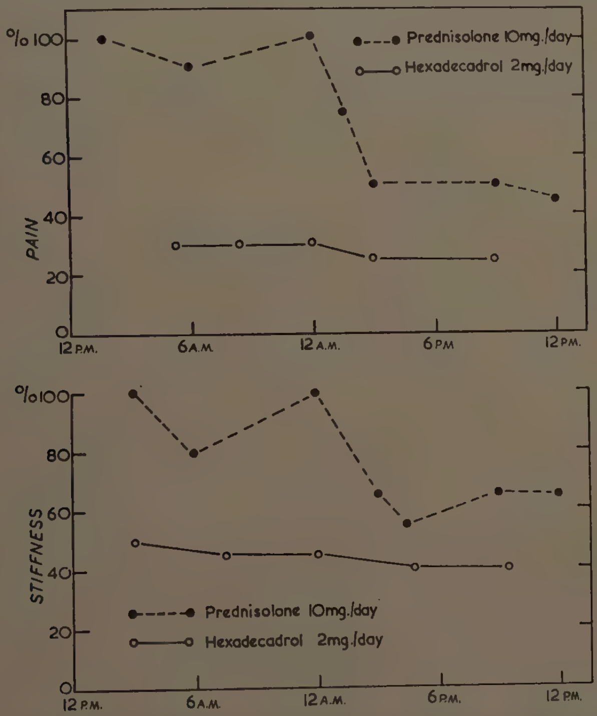

FIGURE 3. Assessments during one day on prednisolone and on hexadecadrol (dexamethasone).

and, at this dose, obesity and facial mooning were such that long-term administration was becoming difficult. In the first case there was good suppression with a dose ratio of dexamethasone to prednisolone of 1:6, but this tended to be less successful at the end of 4 months' administration.

The second case (a patient who has had 4 different steroids in the last 18 months) says, after 4½ months on dexamethasone, that she feels better than she has ever felt. With the third patient we have now achieved good suppression with a dose ratio of dexamethasone to prednisolone of 1:3 but, after 2 months, she still has well-marked facial mooning. We have 1 case whose unusual skin sensitivity has been overcome with dexamethasone. This woman, 33 years old and with a 7-year history of rheumatoid arthritis, developed severe acne of the face and chest on 10 U. of corticotrophin. With prednisolone the acne persisted and with cortisone severe skin irritation occurred at 37.5 mg./day, which was inadequate to control arthritis. Three months ago this patient was shifted to dexamethasone and, since then, there has been no acne or irritation and her arthritis is well suppressed with a dose of 2.8 mg./day.

We were anxious to observe the effect of the new analogue on glycosuria and administered it to a patient with polyarteritis nodosa who required a high steroid dosage. The patient had developed a diabetic curve on 35 mg./day of prednisolone and reverted to normal when shifted to 7.2 mg./day of dexamethasone. A further change to 36 mg./day of triamcinolone produced a relapse (FIGURE 4).

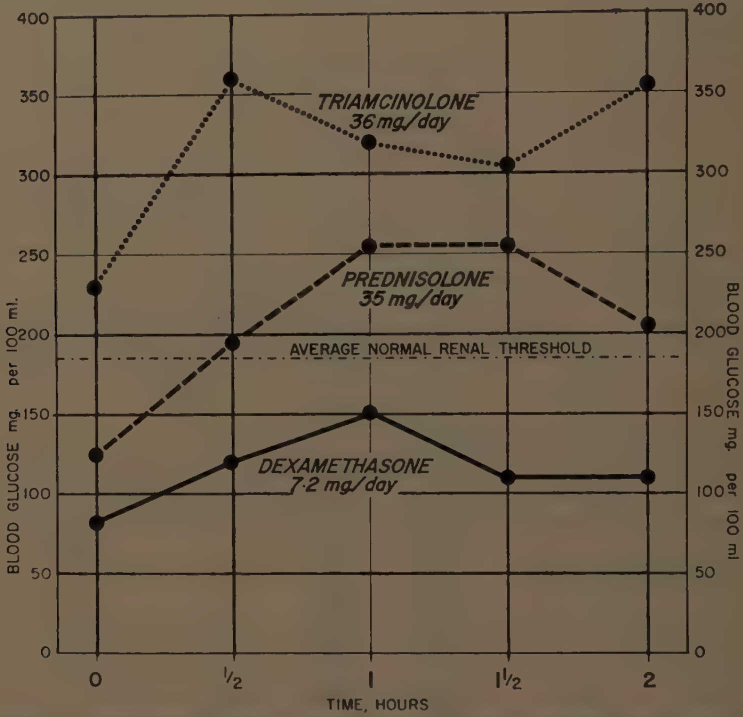

FIGURE 4. Comparative glucose tolerance tests in a case requiring a high steroid dosage Patient W.T., 47 years old, with polyarteritis nodosa.

George Fearnley at the Gloucester Royal Infirmary, has studied a number of cases from a different standpoint. In 6 patients dexamethasone was the first steroid used and, in a dose of 0.75 or 1.5 mg., there was a good suppressive effect with a satisfactory increase in grip and a slight fall in sedimentation rate. In 3 of these cases mooning of the face occurred, with increase of weight after a few weeks. Dyspepsia was clearly present in a number of cases; 2 with severe indigestion were shifted to dexamethasone to see if there would be less gastric irritation but the change had no effect and, in 1, a pyloric ulcer that had been healed recurred.

The problem of comparing one oral steroid with another is difficult until the exact strength ratio in clinical practice has been found; until then the scales may be loaded too heavily in favor of one or the other.

There is no particular advantage in having a stronger steroid for, to the patient, it is just another tablet to be taken through the day and, for the physician, minor adjustments of dosage are more difficult.

From our short study we conclude that dexamethasone is a potent anti-inflammatory steroid. We consider that it is about six times as strong as prednisolone. In some patients with rheumatoid arthritis better suppression can be achieved with this drug than with prednisolone and, in others, the effect is not so favorable.

The incidence of dyspepsia was equal with the two drugs. Dexamethasone appears less likely to cause an abnormal glucose tolerance curve when a diabetic tendency is present, and it is useful to have another steroid available that may be more effective in certain severe cases of rheumatoid arthritis.

Our combined study has been too short to allow us any opinion with regard to osteoporosis.

The acceptance of corticosteroids for the treatment of severe active rheumatoid arthritis has been slow in Great Britain. This is partly due to the fact that the drugs have only lately been available to general practitioners and partly to the results of the clinical trials carried out by the Medical Research Council[10] and the Empire Rheumatism Council.[11]

These trials, including large groups of patients with varying degrees of rheumatoid activity, showed no difference between cortisone and salicylates. They did not show, nor were they designed to show, what is needed for a particular patient with severe rheumatoid arthritis who, despite all efforts of the physician, is rapidly becoming crippled.

As a practicing physician having more than eight years experience with corticosteroids, I am convinced that with the severe type of disease these drugs can make a complete difference in the lives of a considerable number of patients. In my experience these steroids have enabled men and women who were regarded as crippled to become independent, to be less of a burden on their families, to regain their morale, and often to return to and remain at their previous occupations.

Now that oral steroids are available to every doctor in our country and are being widely prescribed, it is important that those of us with experience should be realistic about the difficulties of long-term treatment. Much has been written about minor side effects that, in fact, are of little practical importance.

I consider there are three drawbacks to long-term treatment. The first is the fear that someone will stop the drug suddenly in the face of stress such as accident or surgery. This can be overcome by further education. The second and third, as I have already mentioned, are peptic ulceration and osteoporosis. These offer a challenge to the pharmaceutical industry, which is responding by the production of new analogues.

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Discussion of the Paper

RICHARD H. FREYBERG (*Cornell University Medical College and Hospital for Special Surgery, New York, N. Y.*): Splendid reviews by Boland and Savage of the progress in clinical application of improved corticosteroids for rheumatic diseases have been presented. Headaches and heartaches have come to all the clinical investigators in the form of accidents resulting from some of the physiological nonantirheumatic so-called side effects of the corticosteroids. When these accidents happen, the investigator may be discouraged by the potential dangers of corticosteroid therapy. I take heart from recalling the remark made to me by Hench during the first year of this past decade: "Surely it is dangerous and, at times, even with the best known precautions, accidents will happen, but we can't give up." It is much like the exploration of the possibilities of jet air travel and guided missiles—tragedies may occur, but the research must go on and somebody must do it; otherwise, what progress can we make?

Of the newly synthesized corticosteroids, several have good anti-inflammatory, antirheumatic capacity. Changes in structure have tended to increase the potency of the corticosteroids but, as pointed out by Savage, this increase in antirheumatic potency is not important medically except in relation to the side effects. As Boland emphasized, the important question is whether the amount of anti-inflammatory corticosteroid needed to suppress the rheumatoid activity can be tolerated without important undesired effects. It is gratifying that the chemists have been able to produce cortisone derivatives that distinctly lessen many side effects and virtually eliminate a few, such as troublesome sodium retention and edema. However, as stressed by Boland, the greatest problem remaining is elimination of the mysterious ulcerogenic capacity, the catabolic effects producing osteoporosis and resulting fractures, and vasculitis. There is a real sex-related difference in frequency and severity of these side effects, which present much greater problems in the female. All of these troublesome side effects assume greater importance in the rheumatoid patient because of the necessity for prolonged administration of corticosteroids in this chronic disease. I strongly endorse the policy, stated by both authors, that presently available corticosteroids should not be routinely administered to all patients with rheumatoid arthritis; many do not need this potent therapeutic agent. Candidates for corticosteroid therapy always should be carefully selected. In addition to selecting the patient to be treated, the physician must also decide which corticosteroid he will use. Again I emphasize that it is not the antirheumatic potency of the preparation but the difference in its side effects that should govern this selection. For the edematous individual a sodium nonretainer is the obvious choice; for the overweight person with easily stimulated appetite the nonappetite-stimulating triamcinolone may be preferable; for the thin rheumatoid arthritic patient with a poor appetite, hydrocortisone, prednisolone, or dexamethasone may be superior.

One practical use of corticosteroids (not mentioned in the previous papers) is intra-articular injection for local anti-inflammatory effect. This is of distinct value in properly selected individuals and the pharmaceutical manufacturers are constantly improving the preparations made available for this purpose.

During the next decade, it seems quite clear, chemists will be striving more diligently to produce corticosteroids with less unwanted effects and even to isolate effects in separate corticosteroids; the physiologists and the pharmacologists will be attempting to learn by what mechanisms the corticosteroids produce their effects in connective tissue; and the clinical investigators will busy themselves in the study of the nature of rheumatoid arthritis and how best to use the newly developed agents in practice.

The past decade has been a most exciting and rewarding period in medicine and the clearly allied pharmaceutical field. It is hoped and expected that the excellent start will continue through succeeding decades until the problems of rheumatic disease are solved.

CHARLES SLOCUMB (*University of Minnesota* (*Mayo Foundation*) *and Mayo Clinic, Rochester, Minn.*): I think that we have all seen a considerable number of undesirable effects, and I cannot be quite as optimistic about the relative safety of accepting them as has been suggested. Certainly, a good many of the undesirable effects lead only to moderate inconvenience, but there is a need for a study of the occurrence of vascular lesions, periarteritis, and acquired LE reactions and, as Freyberg mentioned, this can lead to a better understanding of this whole group of diseases. It does not strike me as especially frightening; it is simply another challenge.

PHILIP S. HENCH (*University of Minnesota* (*Mayo Foundation*) *and Mayo Clinic, Rochester, Minn.*): What is your own experience—and it may differ from that of others—regarding the incidence of peptic ulcer in steroid- and nonsteroid-treated rheumatoids?

EDWARD W. BOLAND (*St. Vincent's Hospital, Los Angeles, Calif.*): In our experience, the incidence of peptic ulcer is greater among patients receiving long-term steroid therapy than in rheumatoid patients not being treated with steroids. Furthermore, the incidence has been found to be greater with the delta-1 steroids than with the naturally occurring hormones, hydrocortisone and cortisone. The contention that the ulcerations found on routine roentgenographic examinations are etiologically related to steroid therapy is strengthened by the fact that the majority have been located in the prepyloric region, a site that is not the most common one for ulcers in the general population.

HENCH: Would Savage give us a comment on the incidence he has seen?

OSWALD SAVAGE: I do not know the incidence in rheumatoid arthritis not treated with steroids but, of course, ulcers do occur. I tried to make the point that the problem is not so much the fact that the steroid-treated cases may develop ulcers, but that the ulcers may bleed or perhaps perforate without any previous symptoms. However, I think one important aspect is that my colleagues in Great Britain tell me that they do not see ulcers in nonrheumatoid arthritic patients who have been on long-term steroid treatment. For example, patients with ulcerative colitis who have been on long-term steroid therapy do not get ulcers, and patients who have had adrenalectomy for cancer and have been on maintenance steroid therapy do not get peptic ulceration. I wonder whether there may be a clue in this for us.

HENCH: We believe that there is a definite connection between ulcers and rheumatoid arthritis.

THE MANAGEMENT OF ALLERGIC DISORDERS WITH ANTI-INFLAMMATORY STEROIDS

B. Rose, E. McGarry, A. Knight
The McGill University Clinic and the Division of Allergy, Royal Victoria Hospital, Montreal, Canada

The introduction of cortisone and corticotropin as agents capable of suppressing the signs and symptoms of a wide variety of clinical states marked one of the great advances in medicine. In no other group of conditions have these agents been used as extensively as in the allergic disorders, probably because of their high incidence and apparent ease of control. However, reports have appeared that expressed a considerable divergence of opinion concerning the basic value and potential dangers of the steroids. Thus, some appear to use them with little fear of undesirable effects, whereas others have condemned them almost without reserve.[1, 2] Such variations of opinion are understandable when it is recognized that their basic mechanism of action is still obscure, that symptoms will usually recur after the drugs are withdrawn, and that continued use may lead to a variety of undesirable effects, some of which may be fatal.

It is the purpose of this presentation to review the general results in a group of 590 patients, mostly asthmatics, observed during the past 10 years. Since the progress made in modifications of structure and pharmacological properties are described in detail elsewhere in this monograph, it will not be referred to here.

The study was begun in 1949 when our first group of cases was treated with corticotropin; this was described in a preliminary report in 1950.[3] From the outset, a number of procedures was followed to evaluate the effects of hormone treatment; these included respiratory-function studies, glucose tolerance tests, and skeletal surveys for evidence of osteoporosis. In some hospitalized patients, metabolic balance studies were carried out. In these as well as in others, adrenocortical function was evaluated by measurement of urine 17-ketosteroids and 17-hydroxycorticoids and blood corticoids. The changes in these parameters have been used as an index of the response of the adrenal gland to ACTH. While it is possible to follow patients clinically without benefit of these more elaborate laboratory procedures, considerable information has accrued from such studies. Only a general evaluation can be made here; the more detailed results will be presented elsewhere.

In general, steroids should not be used in any situation in which signs and symptoms can be controlled by more conservative therapy. This has already been discussed in more detail, as have the contraindications to steroid therapy.[4] This report deals for the most part with experiences encountered with patients on long-term therapy. Precautions and contraindications are relative and need not be considered in those situations in which steroid therapy may be lifesaving. Once the decision to use steroid therapy has been made, better results will be obtained if large doses are used initially. Usually, the more rapidly symptoms are brought under control, the sooner the dose of steroid can be decreased and gradually withdrawn.

A general statement may be made concerning available anti-inflammatory agents in terms of therapy in allergic diseases (TABLE 1). With the exception of 9-alpha-fluorohydrocortisone, all may be used orally. By and large, cortisone and hydrocortisone are reserved for those patients in whom a hypoadrenal state with poorly responding adrenals may have resulted from prolonged therapy. Although not all may agree with this, since Compound F, or hydrocortisone, is the major steroid elaborated by the human adrenal cortex, this compound is believed to be best where a physiological rather than a pharmacological effect is required. Clinically, as well, it appears that such patients are maintained better with these compounds than with the newer modifications.

If this relatively small group of patients is eliminated, there remains the choice of compound in terms of possible undesirable effects and the clinical response of the patient. Generally speaking, the newer compounds are more potent, weight for weight; in addition, they do not tend to produce as marked undesirable effects as do the older compounds such as cortisone and hydrocortisone. Such improvements as lack of effect on salt and water metabolism have tended to reduce the need for salt restriction and potassium supplements, although the latter, in some cases, may still be required. All other undesirable effects such as mooning of the face, hirsutism, osteoporosis, and impairment of carbohydrate tolerance can and do occur with the newer compounds. This is to be expected with any agent possessing glucocorticoid properties. Increased appetite and weight gain may occur with some, such as prednisone and prednisolone, whereas the opposite tendency is often, but by no means constantly evident with triamcinolone or 6-methylprednisolone (Medrol). The need for caution and the recognition of contraindications are of paramount importance in the use of these compounds in a general way. It is a wise clinician who can prognosticate which patient will not develop some serious consequence of therapy.

TABLE 1

ORALLY ACTIVE STEROIDS FOR THE MANAGEMENT OF ALLERGY

Steroid	Strength (mg.)
Cortisone (17-hydroxy-11-oxycorticosterone)	25
Hydrocortisone (17-hydroxy-11-dehydrocorticosterone)	20
Prednisone (delta-2-4-cortisone)	5
Prednisolone (delta-2-4-hydrocortisone)	5
Triamcinolone (9-alpha-fluoro-16-hydroxyprednisolone)	4
Medrol (6-methylprednisolone)	4
Dexamethasone (9-alpha-fluoro-16-methylprednisolone)	0.7

Emergencies in which hormone treatment is indicated are listed in TABLE 2. In most of these, since it is impossible to ascertain the response of the adrenal gland, it is usually essential to use a soluble form of steroid that may be given intravenously, such as Solu-Cortef (hydrocortisone hemisuccinate), prednisolone hemisuccinate, or triamcinolone hemisuccinate, in preference to corticotropin. Of course, if the patient can swallow, then oral steroid therapy is almost as good, since these compounds are absorbed rapidly from the gastrointestinal tract. It is important in all of these conditions to recognize, where indicated, the need for adjunct treatment such as hydration, antibiotics, oxygen, and bronchodilators. It is particularly important to realize that these intravenous steroids may not control the symptoms immediately. Consequently, adrenaline should be used and, if vasomotor collapse is a major feature, noradrenalin will be required intravenously to restore and maintain blood pressure until such time as the patient seems capable of maintaining it without help.

The necessity for intravenous administration generally ceases after the first 6 to 24 hours since, by that time, the patient can usually take oral medication or control can be maintained by the intramuscular route; again, this depends on circumstances. When intramuscular preparations are used, the initial dose should be the equivalent of at least 300 mg. of cortisone acetate every 24 hours. It is also important to remember that 24 to 36 hours elapse before the intramuscularly injected steroid takes effect. As with all other conditions, once the disease is under control, slow withdrawal should be started.

Table 2

Indications for the Use of Hormones

Lifesaving emergencies
Acute status asthmaticus
Exfoliative dermatitis
Pituitary adrenal suppression due to previous therapy
Acute drug reactions
Acute serum sickness
Polyarteritis

Table 3

Indications for the Use of Hormones

Self-limited conditions
Seasonal rhinitis (severe)
Seasonal asthma (severe)
Some forms of acute urticaria and angioedema
Spreading contact dermatitis
Loeffler's syndrome (eosinophilic pneumonia)

By far, the conditions most responsive to treatment are those listed in TABLE 3. Since these are usually self-limiting, one can count on withdrawing treatment without consequent relapse.

The conditions most unresponsive to treatment and yet often the most needy are those in the chronic intractable category (TABLE 4), for here it is often necessary to continue steroids for many years.

Since 1949 we have administered steroids or corticotropin to 590 patients, the majority of whom had asthma. The serious complications that resulted in this series are listed in TABLE 5. There were 17 deaths; of these, only 2 could be definitely related to hormone therapy (TABLE 6). The first was a male, aged 56, who had been given ACTH by his physician and told to use it as needed. He was admitted in 1951 to the Royal Victoria Hospital with an acute unrecognized bronchopneumonia, and died in 36 hours. The second was a patient who had been followed for 5 years. At first he had asthma with a bilateral stenosis of his main stem bronchi, which was more marked on the left side. During the 5 years, he developed diabetes insipidus and progressive blindness, and died after removal of a suprasellar tumor; death was due to respiratory failure. Although he had had no steroids for several months, he was not primed with cortisone, and it is probable that this contributed to the postoperative collapse. However, in this group of 590, approximately 30 patients have undergone various forms of surgical procedures, ranging from abdominoperineal resection to simple D. & C., without difficulty, although all were prepared with steroids as discussed below.

Seven of the deaths may have been due to suppression of the pituitary adrenal axis. Three of these occurred at the Royal Victoria Hospital, but the data are insufficient to determine the cause of death. The remaining four died elsewhere and, again, there can be no certainty of the cause. The remaining eight cases died of some other disease or complication clearly unrelated to steroid therapy. Even so, the mortality rate is less than 3 per cent, certainly no higher than the average for asthma before the era of steroids.

Table 4

Indications for the Use of Hormones

- Chronic intractable states
  - Chronic asthma with or without bronchitis
  - Chronic serum sickness
  - Polyarteritis
  - Certain forms of atopic dermatitis

Table 5

Steroid Therapy in Hypersensitivity

No. of patients	590
Deaths	17
Osteoporosis	9
Diabetes	6
Perforation	1

Table 6

Deaths in Relation to Steroid Therapy

Related	2
Possibly related	7
Unrelated	8

Osteoporosis

Nine cases of osteoporosis with collapse of vertebrae have been encountered; of these, only 2 were males. The first was a patient with asthma and a mixed arthritis involving all joints. He was afflicted with both diseases, was bedridden when first seen in 1950, and still is crippled with the arthritis. However, on maintenance with steroids he was able to move about. This was the first patient to develop root pain as a result of compression fracture; he has since suffered two more episodes, with bone grafting necessary after the second one.

The second male patient, aged 58, had been a robust individual, had been confined to bed for severe intractable asthma for 3 months when first seen, and had been maintained on ACTH. Collapse of 3 vertebrae occurred 6 weeks after beginning ACTH and 3 months after the onset of asthma.

The remaining 7 patients, all females, were in the menopausal age group and, as such, would be prone to osteoporosis even if not receiving steroids. Their pain was readily controlled by means of the administration of orally active androgens and estrogens. It is difficult to say to what degree osteoporosis is aggravated by steroid therapy. Certainly, in the postmenopausal female this complication should be observed very closely. In addition, certain patients are more prone to develop osteoporosis than are others, for reasons that are not clear.[5] Fractures in the extremities due to trauma heal in the usual expected time of 6 to 8 weeks in spite of continued steroid therapy; there were 2 patients with such a response in the group.

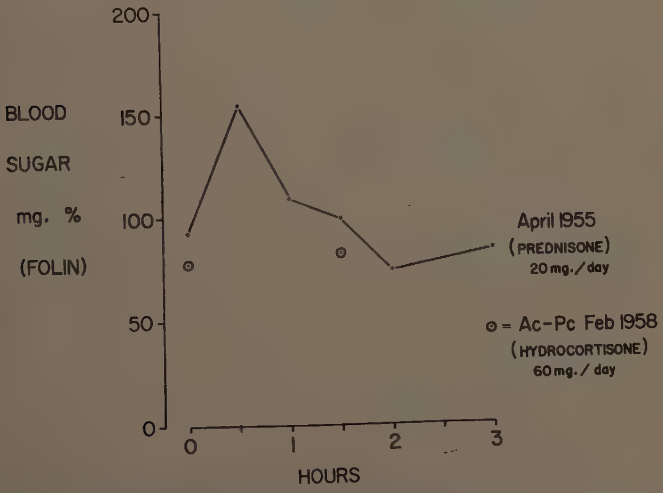

FIGURE 1. Glucose tolerance of patient receiving steroid therapy. Patient J.F., male, 48 years old, suffering with asthma, began treatment July 1950.

Diabetes

Impaired glucose tolerance on maintenance steroid therapy has been observed in 33 patients of the group. Of these, straightforward diabetes mellitus was discovered in 5. All had family histories of the disease; in some, impairment of the glucose tolerance had been established prior to the initiation of steroids. Four are maintained on diet and insulin, and there is no evidence that the disease has been aggravated, even after 9 years of constant steroid maintenance. The chief difference between those with true diabetes and those with steroid diabetes lies in the fasting blood sugar, which is usually within normal limits in the latter group.

Contrasted to this are those many patients who have no abnormality in glucose tolerance in spite of years of maintenance therapy; an example of this is shown in FIGURE 1. An example of steroid diabetes without glycosuria or the need for dietary control or insulin is shown in FIGURE 2. By and large, therefore, diabetes has not proven to be a major problem and is just as easily controlled in steroid-maintained patients as in the nonsteroid-maintained.

Massive Collapse Due to Pituitary Adrenal Suppression and Infection

Although many of the undesirable effects of steroid therapy are of minor and transient consequence, one of the most difficult and sometimes fatal (if not recognized and treated promptly) is that taking the form of adrenocortical collapse with widespread infection and asthma. These reactions are usually found in patients who have been maintained for lengthy periods on anti-inflammatory steroids. The syndrome may appear suddenly when infection occurs or, occasionally, without infection after withdrawal of the steroid has been achieved.

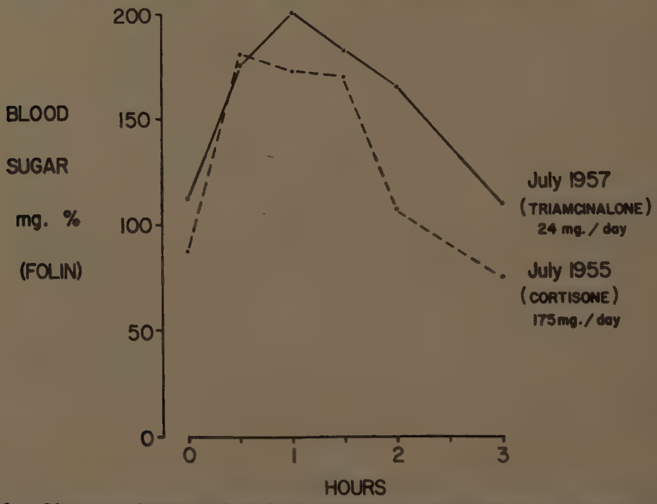

FIGURE 2. Glucose tolerance of patient receiving steroid therapy. Patient A.H., male, 64 years old, suffering with asthma, began treatment February 1951.

Such was the case in the patient whose course is illustrated in FIGURE 3. Treatment with steroids had been stopped for 6 months when she developed a bilateral bronchopneumonia and was admitted to hospital in acute collapse. The course of treatment illustrated on the chart shows that blood pressure could not be maintained by intravenous Solu-Cortef alone, but that noradrenalin was required in the initial stages.

The suppression of both pituitary as well as adrenal function by long-term steroid therapy has been emphasized by others; pertinent to this are the findings of Burrage *et al.*,[1] who observed morphologic signs of atrophy of both adrenals and pituitary at autopsy of patients who had been on long-term steroid therapy. However, it has become clear that there is a great variation in the ease with which such changes may arise. For example, the patient whose course is shown in FIGURE 3, on subsequent examination was found to be virtually unresponsive to an ACTH test in terms of both blood- and urine-steroid assays. Other patients on therapy for at least an equal time may show normal or moderately impaired activity. More recently, because of this variation in responsiveness such assays have been made in patients prior to beginning hormone therapy, and there is some evidence that impairment of pituitary adrenal function as measured by such a procedure is present in some severe asthmatics who have never received steroids.

Since it is not possible to determine in which patients the pituitary adrenal axis has been suppressed, it has been our practice to regard all individuals who have received steroid therapy as potential cases of adrenal insufficiency, and to treat them accordingly in stressful situations. For elective operations, 100 mg. of cortisone acetate is given intramuscularly twice daily for 3 days, beginning 48 hours before operation. This is followed by 100 mg. of cortisone acetate intramuscularly on the first postoperative day, and then by oral therapy with any active steroid, which is then slowly reduced. Solu-Cortef is kept at hand during the operation and for the first 3 postoperative days.

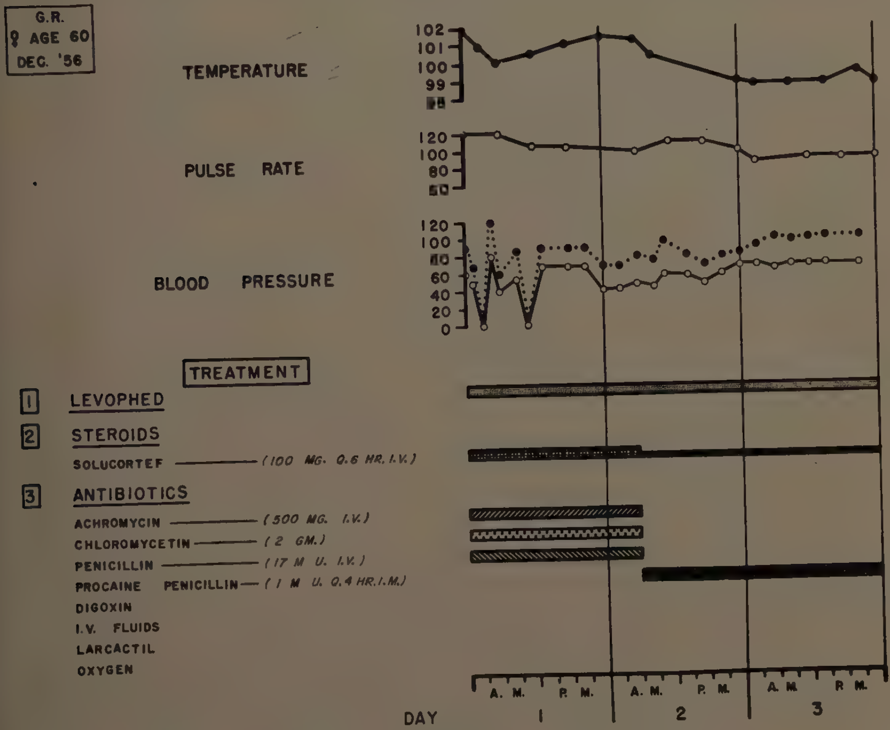

FIGURE 3. Collapse due to infection after steroid therapy.

Intravenous steroid therapy is used for acute emergencies, 100 mg. of Solu-Cortef being given in the first 5 min., followed by a slow drip containing 100 mg. of Solu-Cortef at a rate providing 10 to 15 mg./hour. Intramuscular therapy is also started if it appears that the patient may not be capable of taking oral therapy within 36 hours.

Other Side Effects

There are a variety of undesirable side effects such as moon facies, hirsutism, ecchymoses, dependent edema, psychoses, peptic ulcer, and hypertension. While all have been observed at times, the incidence has not been large in this series of patients. Mooning of the face and the appearance of a buffalo hump can occur with corticotropin or any of the orally active anti-inflammatory steroids if they are given in a sufficiently large dose for a long period. However, the tendency for this to occur with the newer compounds such as triamcinolone, dexamethasone, or 6-methylprednisolone is considerably less than with cortisone, cortisol, or corticotropin. This is also true of dependent edema (due to salt and water retention) and the tendency to enhanced potassium excretion. Hypertension is not as much of a problem today, except in those cases with the malignant form, infrequently seen in patients with asthma. A noteworthy point is that the blood pressure in many cases of asthma, elevated during attacks, will promptly subside when the attack is relieved, regardless of whether the means used included the steroids.

Gastric irritation and gastric or duodenal ulcer have not been a major problem in this series. When encountered, the condition is easily relieved by antispasmodics, antacids, and a dietary regime with maintenance of steroid. Only 1 patient in this series developed perforation; she has periarteritis and was first seen in 1950 when she was admitted to hospital in the acute stages of the disease. At that time she was placed on 100 mg. ACTH daily. Perforation occurred, and she was operated on while maintained on the same dose of hormone. She has since been given all of the various orally active compounds including cortisone, cortisol, prednisone, prednisolone, triamcinolone, Medrol, and dexamethasone; best maintenance is achieved with 20 to 30 mg. prednisone per day. There has been no recurrence of the gastrointestinal symptoms. Of the newer compounds, triamcinolone has induced nausea in a small number of patients, including the one just described. Weakness and a feeling of uncertainty has occurred in others receiving dexamethasone, but again the incidence is small.

An increase in bruising and ecchymoses occurs in some female patients with apparently greater ease when the modifications of prednisolone are used. In some the tendency has decreased or disappeared when Medrol, dexamethasone, or triamcinolone was replaced by prednisone. The nature of the increased capillary fragility is not clear; coagulation studies have shown normal limits and we have encountered no thromboembolic phenomena.

Long-Term vs. Short-Term Therapy

It is difficult to make a comparative evaluation of the virtues of long- and short-term therapy. Obviously, if a patient requires but 1 course of steroids (this seems to be all that is necessary in many cases), and provided that other ancillary means of management are used, then many of the hazards of long-term therapy can be avoided. However, with that patient who requires continuous steroid treatment the question arises of whether one should administer steroids for 2 to 3 weeks, taper slowly, stop, and then resume with a high dose when symptoms reappear, or whether one should determine a maintenance requirement and keep the patient on such a dose continuously. There are points in favor of both methods. It is believed by some that, with intermittent therapy, adrenal suppression is less likely to be as marked, although there is no good evidence to support this contention. The chief virtue of such a procedure is that the patient may be able to quit the steroid for a longer period than may have been thought possible. However, most patients are loathe to adopt this method since they are always incapacitated either as soon as the drug is stopped or within a few days.

In this connection, the question of priming the adrenal gland may be considered. Some believe that the injection of corticotropin at intervals helps to maintain adrenocortical function. While this may be so, the effect is of a temporary nature and, once the corticotropin is withdrawn, adrenal suppression begins again. Furthermore, it does not matter whether corticotropin or steroids are administered for, in both cases, pituitary suppression occurs. In our opinion, therefore, there is little virtue in this procedure.

Finally, there is the question of withdrawal. Is ACTH easier to withdraw than orally active steroids? Some authors believe that it is,[6] but our experience does not substantiate this. Withdrawal is achieved readily in some patients and is very difficult, if at all possible, in others. It does not seem to matter whether one uses corticotropin or orally active steroids.

Discussion

It has been intimated throughout this presentation that, in terms of undesirable effects, the response of any subject to the administration of any of the orally active anti-inflammatory steroids is quite variable. Relative to the number of patients treated with steroids in the group studied by us, the incidence of any one complication is not unduly high. It seems clear, furthermore, that these compounds tend to accentuate a pre-existing tendency in certain patients, even when used in low dosage. In view of this, diabetes may be disclosed or a tendency to osteoporosis enhanced in patients treated with steroids.

In some careful metabolic-balance studies, we have shown that triamcinolone and 6-methylprednisolone do not alter electrolyte balance and, of more significance, calcium balance does not appear to be adversely affected. These studies will be published elsewhere. Thus, as the steroids are modified, it is to be hoped that, ultimately, an ideal compound may be made available. However, it is to be emphasized that the abandonment of all orthodox methods of treatment in favor of the easy use of steroids for the control of allergic disease cannot be condemned too strongly. A large percentage of patients with allergy can be managed without benefit of steroids.

Finally, it should be pointed out that anti-inflammatory steroids are useful and acceptable means of treatment in patients who have failed to respond to all other forms of therapy. It is clear, furthermore, that judicious management, keeping the dose as low as is compatible with freedom from symptoms, and the use of adjunct forms of therapy have permitted many chronic invalids to return to a useful way of life. To give a patient anti-inflammatory steroids without advising him of the nature of the compound and without adequate and frequent follow-up is to do him an injustice that may lead to serious consequences.

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Discussion of the Paper

Philip S. Hench (*University of Minnesota (Mayo Foundation) and Mayo Clinic, Rochester, Minn.*): I should like to ask one question. Presumably, you do not have many withdrawal reactions in your private practice; nevertheless, you have heard of them and have seen some for various reasons. How often do you see in the allergic patients a withdrawal reaction associated with a rheumatoidlike flare?

Bram Rose: Do you mean the typical withdrawal syndrome?

Hench: Yes, how often among the allergic patients in whom you suspect no rheumatic component or complication would you have a withdrawal reaction, and do you see some articular manifestations in addition to the allergic-type withdrawals?

Rose: Articular manifestations do occur but, in my experience, they are very rare, indeed. I can recall seeing them in about three patients, but no more.

Hench: Do you remember whether in those patients there was any history of previous articular manifestations or whether there were any arthritic symptoms subsequent to the withdrawal reaction, suggesting that the patient had a latency?

Rose: No, there were no past or subsequent articular symptoms, although we have looked for them.

Joseph J. Bunim (*Johns Hopkins University School of Medicine, Baltimore, Md.;* and *National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md.*): Many of us have come to believe that there may be an association between the undesirable side effects from steroids and the disease for which the patient is being treated. For example, patients with rheumatoid arthritis who never receive steroids seem to have a higher incidence of peptic ulcer than nonrheumatoid patients; or some patients with rheumatoid arthritis already have, as a result of their disease, osteoporosis, which other patients do not have. Therefore, it is not surprising to observe that, following prolonged administration of these corticosteroids, a relatively high incidence of peptic ulcer and compressed fractures occur in patients with rheumatoid arthritis. It would be of considerable interest to us to know the relative incidence of these same undesirable side effects in patients suffering from allergic conditions and who have been on equally prolonged steroid administration. Another question that arises concerns polyarteritis nodosa: rheumatoid arthritis patients unquestionably develop polyarteritis nodosa even without receiving steroid therapy, yet I think it is clear that in steroid-treated patients the percentage is higher than in the nonsteroid-treated, although valid statistics have not yet been collected on this point.

These are the things we are most interested in knowing from Rose: What are the relative incidences of peptic ulcer, compressed fractures of the vertebrae, and polyarteritis nodosa during the course of prolonged corticosteroid therapy in patients suffering from allergic conditions and in those suffering from rheumatoid arthritis?

Rose: All I can say is that I cannot answer these questions now. We are surveying the literature and getting as much information from others as we can. As I have said, we found an incidence of osteoporosis in 7 patients in 590, which would be about 1 per cent.

As far as the pertinent question of peptic ulcer is concerned, we have seen very little and we have taken X rays when we thought it necessary; but, of course, one can fall into the trap presented by a silent ulcer. Nevertheless, we have had no acute episodes in this series.

Another disease in which we are interested is diabetes. I have always thought that diabetes and asthma were mutually exclusive, and Joslin notes that the incidence of asthma in diabetes is extremely small. However, we have seen patients with severe asthma develop diabetes without ever having received steroids. Furthermore, as the diabetes became more severe, the asthma completely disappeared. Others seem to have made similar observations, although this is purely rumor.

With reference to the polyarteritis, I think that the answer to this will undoubtedly appear as soon as we know more about the congeners that are being prepared. It is quite conceivable that, as one shifts the patient from one steroid to another, one may, for example, inhibit the particular fraction elaborated by the patient's adrenal gland that is responsible for the suppression of the disease. Thus, if a steroid inhibits that particular fraction, then obviously the disease may be aggravated. However, as far as polyarteritis is concerned, the question is even more mystifying because, as you know, there are those who respond well to the steroids and those who do not and, in fact, regardless of what one does, go on to die.

THE USE OF CORTICOSTEROIDS IN HEMATOLOGICAL THERAPY*

William Dameshek

*Tufts University School of Medicine and Blood Research Laboratory,
New England Center Hospital, Boston, Mass.*

It may be said that the introduction of ACTH and the corticosteroids into clinical medicine has been productive of what can only be called a revolution in the therapy of hematological disease. When one considers the profound therapeutic effects of these materials in such a diverse group of conditions as acute and chronic leukemia, aplastic anemia, autoimmune hemolytic anemia, and idiopathic thrombocytopenic purpura, to mention but a few, there is at first a feeling of incredulity and then a sense of wonder as to how it had been possible to do without these potent agents. It has been necessary to revise thoroughly the management of at least two diseases: autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP), particularly with respect to splenectomy. In the leukemias, not only do the corticosteroids lend important adjuvant qualities to remedies that are perhaps more specific, but at times these new drugs appear to be specific remedial agents themselves. This report summarizes some of the effects of ACTH and the corticosteroids in clinical hematology and introduces some speculations on their mode of action.

Our interest in ACTH was first attracted by the fundamental observations of Dougherty and White,[1] who showed that this material, when administered in sufficient dosage, resulted in a reduction in the size of lymphoid tissue, apparently on the basis of mitotic inhibition, pyknonecrosis, and cytolysis. This phenomenon suggested the possibility of using ACTH in the treatment of lymphocytic leukemia and related disorders, as already had been suggested by Murphy and his co-workers[2] in their work with experimental animals. In addition, Dougherty and White showed that the reduction in the mass of lymphoid tissue by ACTH was productive of profound changes in the serum proteins, more particularly the globulins, and in the production of antibodies. This effect naturally suggested the use of ACTH and the adrenal cortical steroids in certain immunological disorders such as autoimmune hemolytic anemia. Thus, when ACTH first became available to us in sufficient quantity for clinical trial in 1949, it was immediately tried in two classes of patients: those with acute leukemia[3] and those with the type of acquired hemolytic anemia caused by the development of abnormal antibody.[4] The results were impressive and led to the further use of these two classes of compounds in a variety of hematological disorders. Although nearly a decade has elapsed since this work was first begun, we continue to be amazed at the frequently remarkable effects of these substances in very difficult and diverse situations. The experience gained in the use of these materials in hematological disease during the past decade is the basis of this review.

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Leukemia

Leukemia may be classified as a generalized neoplastic proliferative disease of one of the white cell-forming tissues.[5] The proliferation may be a very rapid, highly malignant one (acute), or it may be relatively slow (chronic). The acute cases, particularly those of childhood, were shown, beginning in 1947, to be capable of reversibility with the use of folic acid antagonists. Resistance developed after a time, and no further effects with these substances took place. Our first therapeutic uses of these compounds were in such cases; later, untreated cases of acute leukemia were given ACTH as the first medication;[3] more recently, massive doses of prednisone were employed in adult cases of acute leukemia.[6]

Acute Leukemia

The first patients we treated with ACTH were in an apparently hopeless status, having developed resistance to the folic acid antagonists and showing pancytopenia and hemorrhagic manifestations. Striking effects were noted in some cases: reticulocytosis followed by an increase in the red cell count, an increase in the platelets, a disappearance of abnormal, primitive lymphoblasts and, eventually, a marked improvement in the entire leukocytic picture. There was simultaneous improvement in the hemorrhagic manifestations and a striking "tonic" effect, with a great upsurge in such aspects as energy and vitality and a marked improvement in appetite. Unfortunately, the effects on the blood picture were transitory and, as the patients developed very marked Cushingoid effects and the increasing ravages of the leukemic disease, it became increasingly apparent that these last-ditch therapeutic efforts were of only superficial benefit.

When ACTH was given as the initial medication in dosages of 20 to 80 mg./day intramuscularly to a series of cases,[3] there was, in addition to the marked subjective improvement, a reduction in the fever and, in some cases, a complete reversal in the leukemic process. In 5 of 8 consecutive cases in which remissions occurred, there were "extraordinary rises in reticulocytes and platelets, simultaneously with evidence of great bone marrow activity on the part of red cell and platelet precursors."[3] At times, persistent therapy was followed by a progressive reduction in the acute lymphocytic variety of childhood; cases of the acute granulocytic variety seemed, if anything, to react adversely to ACTH therapy.

In contrast to the relatively brief remissions induced by ACTH, those obtained with the folic acid antagonists were of much longer duration. By combining the folic acid antagonists therapy with ACTH it was possible to obtain remissions in approximately 75 per cent of the childhood cases. However, the remissions, although complete, were always temporary, and further remissions were increasingly more difficult to obtain.

Adult acute leukemia, in contrast to the childhood variety, was usually resistant to both steroid therapy in the ordinary dosages and to the folic acid antagonists, although some cases (approximately 10 per cent) were beneficially affected by the use of 6-mercaptopurine (6-MP). With the advent of prednisone, which could be given in large dosage without danger of excessive water and sodium retention and potassium depletion, massive doses of this newer corticosteroid were used in a consecutive series of adult cases.[6] All of these patients were above the age of 30 and had the granulocytic variety of the disease. The first series of 10 cases was given prednisone in a dosage of 1000 mg./day and, if possible, for a period of 2 weeks. In the second series of 10 cases, 250 mg. of prednisone was given daily for 2 weeks, with smaller doses after the initial period of massive dosage.

With the use of 1000 mg. of prednisone, 3 cases developed varying degrees of psychosis, which made it necessary to terminate further use of the drug after 7 to 10 days; however, there was no water retention; in fact, a rather paradoxical diuresis was established.* Three of the cases developed complete remissions, one lasting for 8 months and a second for 5 months; a third case continues in complete remission after 3 years. With the use of 250 mg. of prednisone daily, 3 complete remissions were again obtained of 10 cases treated; of these 10 cases, 2 had histories of duodenal ulcer, but no apparent activation of the ulcer took place. Care was taken, however, to give the patients tincture of belladonna before meals and an aluminum hydroxide gel after meals. No serious reactions developed with this large dose given for a 2-week period, following which the dosage was gradually reduced to 100 mg., then to 50 mg. daily, with eventual maintenance at 25 to 50 mg. daily.

From the use of these relatively massive doses it was clear that complete reversal of the highly malignant acute leukemic process was possible, and with results that were as good as, if not better than with the antimetabolite 6-MP. The results, with the exception of one case, however, were always temporary (from 3 to 8 months), resistance occurring eventually, as with the antimetabolites. It was also clear that the previously noted adverse effects (with small doses) in acute granulocytic leukemia were not present. Thus, the pharmacological effect apparently differed from the physiological one. Further trials of prednisone in smaller initial doses (50 mg. or 100 mg./day) indicated that, although these doses might have a temporary beneficial effect, they did not result in complete remissions.†

Interpretation of these results in acute leukemia could lead only to the conclusion that ACTH and the corticosteroids were, at least in large doses, antiproliferative agents. This conclusion is in line with previous data indicating that these substances are antimitotic, at least with certain tissues, such as lymphoid tissue. In relatively physiological doses, however, the corticoids may be stimulatory, particularly with respect to myeloid tissue.

Chronic Leukemia

Well-defined reductions in lymphoid masses in chronic lymphocytic leukemia were described shortly after ACTH and the corticosteroids were introduced.[7] In the relatively physiological dosages used (100 to 200 mg. cortisone and 20 to 40 mg. prednisone daily), the effects were inconstant and quite temporary. The usual effects, aside from the subjective one of improvement in appetite and vitality, were limited to a slight-to-moderate reduction in lymphadenopathy and, possibly, in spleen size. The leukocyte count usually increased (as a rule, it doubled) during the first month of therapy, followed by a subsidence to previous values. There appeared to be no particular value in treating chronic lymphocytic leukemia with the corticosteroids, except perhaps in an adjuvant fashion; that is, to improve appetite and well-being or to reduce bleeding from thrombocytopenia, especially when other apparently better therapeutic methods were available, including X rays and the chemotherapeutic agents triethylene melamine and chlorambucil (CB 1348, Leukeran). This rule had two exceptions, however. In those cases of the disease with coexistent autoimmune hemolytic anemia (see below) it was possible to produce striking and well-maintained hematological responses indefinitely with the continued use of the corticosteroids. This led to the virtual abandonment of other therapeutic measures, including splenectomy, in the cases with the combined leukemic-hemolytic disturbance.[8] More recently, the remarkable effects of large doses of steroids in cases of lymphoproliferative disease that had become refractory to ordinary methods of therapy have become evident.[9]

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* This reaction was studied in our laboratory by A. Ruzić of Belgrade, Yugoslavia, who concluded, on the basis of clinical and experimental investigations, that this was a diabetes insipiduslike effect induced by a direct pharmacological effect of the hormone on the pituitary.

† Recently, several complete remissions have occurred following the use of prednisone, 125 mg./day.

There are certain cases of widespread and striking lymphoproliferative disease in which large masses of lymphoid tissue are present in peripheral lymph-node-bearing areas, in the spleen and liver, and in various "interior" areas such as in the mesenteric lymph nodes, the mediastinum, the paravertebral nodes, and the retroperitoneal areas. In these cases, satisfactory responses may occur, at least initially, to X-ray therapy or following the use of various alkylating agents (HN_2, triethylene melamine, and Leukeran). As the disease progresses, however, or even early in its course, these agents are no longer effective, or the normal marrow cells are so drastically affected by the continued therapy that severe anemia, granulocytopenia, and thrombocytopenia ensue. Under these circumstances, when further use of these destructive agents is not advisable, the corticosteroids have proved to be of great value.

The use of large doses of prednisone (50 to 200 mg.) in these severe cases of refractory chronic lymphocytic leukemia and disseminated lymphosarcomatosis is often attended by some striking therapeutic manifestations. Huge masses of peripheral and central lymphoid tissue are often greatly reduced and may become nonpalpable within a few months. The spleen gradually recedes in size and also may become no longer palpable. At the same time, the patient, previously in poor health, perspiring, and anemic, shows a rapid subjective and objective improvement. Hemoglobin rises rapidly, platelets rise, and leukocytes and lymphocytes diminish. Within a few months one may be dealing with a patient who appears to be in rugged health. At this time, the dose of prednisone is gradually reduced to a maintenance level of 20 to 25 mg./day. The remission may become complete, or some slight lymphadenopathy or splenomegaly may remain, together with slight blood and marrow lymphocytosis. At this time another course of one of the alkylating agents or irradiation can perhaps be used in the presence of an improved blood picture. The great reductions in lymphoid and splenic masses that often take place indicate an antiproliferative, cytotoxic, or "antimetabolic" effect of the corticosteroid, at least upon certain types of cells, notably the proliferating lymphocyte. In addition, occasional cases of otherwise refractory Hodgkin's disease respond in the same fashion.

Multiple myeloma. This condition, a generalized proliferation of plasmocytes, may be considered as a form of chronic leukemia, that is, chronic subleukemic plasmocytic leukemia. The use of ACTH and the corticosteroids in this disease seemed reasonable in view of the effects of these materials in reducing plasmocytic tissues. Although in some cases a rather marked response took place, the results, particularly when relatively small doses were used, were inconstant. When larger doses were given, more consistent effects took place in the reduction of plasmocytosis with an improvement in all the associated phenomena such as hyperglobulinemia, elevated sedimentation rate, rouleaux formation of the red cells, Bence Jones proteinuria, and anemia. Unfortunately, these beneficial effects were always transitory; indeed, one hesitated to impose long-standing corticosteroid therapy, particularly in large dosage, because of the obvious dangers of osteoporosis and spontaneous fractures. Our usual practice has therefore been to use the corticoids in relatively small dosage (20 to 100 mg. prednisone daily) and chiefly as initial therapy for one to three weeks, then giving urethane. The steroid was then used intermittently, depending upon circumstances.

In summary, we have used the corticosteroids in leukemia for at least six reasons: (1) as specific antimitotic or antiproliferative agents; (2) as adjuvants to the antimetabolites 6-MP and the antifolic agents, either to enhance the antimetabolic effects or as "protective" against the myelotoxic effects of the chemotherapeutic agents; (3) as myelostimulatory agents; (4) as anti-immune substances to attack abnormal antibody production in "symptomatic" autoimmune hemolytic anemia (and in the occasional examples of symptomatic thrombocytopenic purpura and vascular purpura); (5) to reduce the bleeding in thrombocytopenia, perhaps by a nonspecific effect on the blood vessel wall; and (6) to produce important systemic or subjective effects, for example, to reduce the fever, to increase the appetite and sense of well-being, to improve bone pains, and to reduce night sweats. The beneficial effects of ACTH and the corticosteroids in leukemia, particularly when large doses are used, indicate that these agents are antiproliferative (antimitotic and antimetabolic in the broad sense). Their effects on the autoimmune hemolytic process may be on the same basis, that is, due to an antiproliferative effect on the cells concerned with antibody formation. We have lately become impressed with the many similarities between the leukemic process and the immunological one.

The Myeloproliferative Disorders

These disturbances comprise a number of different disorders, the differences being marked in some instances and very slight, if not almost nonexistent in others.[5] The bone marrow, normally an active proliferating organ, but composed of several diverse cellular entities, is itself subject to abnormal or neoplastic proliferative activity in which red cell, granulocytic, megakaryocytic, or reticulum cell groups may participate to a greater or lesser degree. The ensuing syndromes are known as: (chronic forms) polycythemia vera, chronic granulocytic leukemia, myelofibrosis with myeloid metaplasia, and thrombocythemia, and (acute forms) the DiGuglielmo syndrome, acute granulocytic leukemia, and acute myelofibrosis with myeloid metaplasia. Because several cellular lines are often proliferating simultaneously, "transitional" or combined forms are often evident, and an exact diagnosis often becomes difficult and, indeed, perhaps not warranted.

The corticosteroids, which are presumably myelostimulatory, would a priori not be expected to be of any value in chronic granulocytic leukemia, polycythemia vera, thrombocythemia, or myelofibrosis with myeloid metaplasia. In the latter disease, in which fibrosis of the marrow and myeloid metaplasia of spleen and liver are simultaneously present, anemia gradually develops, finally leading to the need for increasing numbers of transfusions. When the transfusion requirement becomes very great, at times up to one unit of 500 cc. blood weekly, the possibility of splenectomy is often discussed, especially since a hemolytic component is almost certainly present. Since this operation is not without danger and has no effect on the continuing severe myelofibrosis, the pros and cons of surgery must be debated very seriously. Finally, once it has been agreed that splenectomy should be done, a trial of one of the corticosteroids should always be made; when this is done a striking beneficial effect not infrequently occurs. In one of our patients, who had been receiving transfusions at the rate of 500 ml. weekly, the use of hydrocortisone led to a complete remission for 1½ years, during whcih no transfusions were required. Eventually, anemia recurred and splenectomy was performed. No further response occurred, the patient dying in a leukemialike state. Less striking remissions have been obtained in other cases of myelofibrosis with myeloid metaplasia, some of them being rather atypical. These results indicate that splenectomy should be postponed until a trial of the corticosteroids has been made. Whether or not the assumption can be made that "if the steroids work, so will splenectomy," is not entirely clear at this time. The improvement that follows corticosteroid therapy is difficult to explain. One may speculate that it is due to stimulation of any remaining unaffected bone marrow tissue or on the myeloid metaplasia itself. Here the corticosteroids may possibly act to aid in the proper maturation or delivery of the red cell elements in the spleen to the circulating blood.

In the other meyloproliferative disturbances, both of the acute (notably, the DiGuglielmo syndrome) and the chronic varieties (that is, chronic granulocytic leukemia, polycythemia vera and thrombocythemia), no appreciable effects with corticosteroid therapy have been noted.

Autoimmune Disorders

The last twenty years have seen the striking development of the autoimmune concept of disease, so that it may be said to include a very broad group of conditions ranging from hemolytic anemia to rheumatoid arthritis and from idiopathic thrombocytopenic purpura (ITP) to systemic lupus erythematosus (SLE). Our first immunohematological studies, which began in 1937, were devoted to acquired hemolytic anemia.[9] Here the presence of abnormal immune bodies appeared to be responsible for the increased red cell destruction, and model experiments to demonstrate this were devised. It became increasingly apparent that an abnormal immunological process might develop within the individual, attacking his own red cells (that is, autoimmune hemolytic anemia). Why the autoantibody developed in the absence of recognizable autoantigen was not clear, but there could be no question that an antibody against red cells was present within the patient's own circulation and that it was being constantly produced, presumably by antibody-producing tissues. Our first therapeutic efforts were limited to splenectomy and, not infrequently, this operation was successful but, in many cases (approximately 50 per cent), the effects were minimal.[10] This result indicated that the effects of autoimmunization could not be completely suppressed by splenectomy, which might indeed remove only a portion of the antibody-producing and red cell-destroying tissues. It became clear that, in order to stop antibody production, it was essential to destroy or at least to reduce the productivity of the entire mass of antibody-producing tissue. The first attempts in this direction were made with nitrogen mustard, a cytotoxic agent acting principally against reticulum and lymphoid cells.[11] The results with this material were inconstant; furthermore, the depressant effects of this agent on the bone marrow seemed to preclude its further use. It was therefore discontinued after only five cases had been treated. When ACTH became available to us in sufficient quantities in 1949, this material was immediately used in several previously splenectomized cases of autoimmune hemolytic anemia and in fresh cases as they became available. The striking effects of the hormone were quickly apparent.

Our initial use of ACTH in autoimmune hemolytic anemia (AIHA) was based on the concept that there was an excessive production of an autoantibody by immunity-producing (that is, reticuloendothelial, lymphoid, and plasmocytic) tissues. The previous work of Dougherty and White[1] indicated a direct effect of ACTH on lymphoid tissues with an apparent reduction in antibody production. Further work by Selye *et al.*[12] indicated more widespread effects of ACTH, not only on lymphoid areas, but also on reticuloendothelial, plasmocytic, thymic, and splenic tissues. It was therefore thought advisable to use relatively large doses of ACTH in the attempt to control antibody production; this approach proved to be successful in most cases. In others, however, extremely large doses (up to 400 units of ACTH daily) were required before a reduction in the hemolytic disturbance became apparent. As definite indications of improvement occurred, the dosage of ACTH was gradually reduced and, eventually, relatively small amounts were given daily. When cortisone became freely available in 1951 and 1952, it was at first used for maintenance therapy and later for the entire course of therapy. As the other corticosteroids appeared (hydrocortisone, prednisone, triamcinolone, and dexamethasone) they were all tried. By and large, the therapeutic effects of these agents were interchangeable, providing adequate dosages were used. From the remarkable results with these agents, it was evident that a revolution in the therapy of AIHA had occurred and that the importance of splenectomy as a therapeutic procedure had now become severely limited.

As noted in previous articles, a well-defined therapeutic response occurred in almost every case in which ACTH or the corticosteroids were used.

The indications of increased hemolysis were quickly reduced, as reflected by reductions in spherocytosis of the red cells, bilirubinemia, fecal and urinary urobilinogen output, prolongation of red cell survival time, diminished necessity for blood transfusions, and reduction in splenomegaly.

The indications of blood production were at first increased, as evidenced by more marked reticulocytosis than previously, leukocytosis, thrombocytosis, and rising red cell count; later, the reticulocyte level dropped to relatively normal values.

The amount of abnormal antibody became reduced. This was apparent at first in the relatively crude titration procedures, which showed a diminution in the circulation of free antibody, then its disappearance. The Coombs test retained its positivity in the great majority of cases, although a reduction in the antiglobulin titer usually took place as treatment was continued. The amount of antibody that could be eluted from the surface of the red cell gradually became reduced, as determined by antibody titration, electrophoretic studies and, more recently, by actual quantitative studies of antibody nitrogen. In all of these procedures it was apparent that the free antibody in the blood serum became reduced first, and that antibody on the surface of the red cell might persist, albeit in very small amounts, for lengthy periods.

Eventually, in most cases, the response was maximal and the hemoglobin and erythrocyte counts rose to normal. In occasional cases corticosteroid could be discontinued without further relapse; in others, relapse occurred. If the eventual dose of corticosteroid for maintenance that was required to prevent relapse was from 5 to 10 mg. of prednisone daily, this dosage might be continued indefinitely. On the other hand, if larger doses were needed, particularly in the elderly, it would become necessary to consider splenectomy seriously because of the possibility of such complications as osteoporosis, peptic ulcer, and diabetes. Ordinarily, no urgency in the ultimate performance of splenectomy seemed necessary.

Studies in the first 40 cases treated in this manner[13] demonstrated that remissions occurred in almost all and that, in about 80 per cent, the remission could be continued with small doses of steroid therapy. In about 20 per cent of the cases it was eventually necessary to perform splenectomy. This might result either in a complete or an incomplete beneficial result; if incomplete, smaller doses of corticosteroid than those previously given were usually necessary. That it was now possible to place 80 per cent of these usually severe cases into complete and sustained remissions with a medical form of therapy was indeed a remarkable event.

The results in the cases of AIHA occurring in association with other more fundamental diseases ("symptomatic" hemolytic anemia) were often equally striking. This was particularly so in the cases of chronic lymphocytic leukemia, in which the AIHA was almost invariably completely refractory to such forms of therapy as X ray, nitrogen mustard, and splenectomy. Excellent responses were also seen in the hemolytic anemia of systemic lupus, periarteritis nodosa, ulcerative colitis, Hodgkin's disease, and so on, provided, of course, there was a well-defined immunological process, as indicated by a positive Coombs test and other serologic abnormalities. If hemolytic anemia was present in conjunction with a negative Coombs test, the results were usually far from good.

These results with immunohemolytic anemia, although they might be explained in different ways, led us to try the steroid hormones in other immunological disorders.

Idiopathic Thrombocytopenic Purpura (ITP)

Work done in many laboratories beginning about 1950 indicated that ITP could be considered as an autoimmune disorder, having many features in common with AIHA.[14] Furthermore, there was increasing indication that splenectomy was by no means the final answer in the treatment of this disorder. The relapse rate of cases adequately followed over a period of years was found to be about 50 per cent. It had, furthermore, become evident that two types of cases could be discriminated: acute and chronic, and that the former was usually a self limited condition.[15] Medical therapy, in the form of ACTH and the use of the newly developed plastic bag transfusions of fresh blood, was found to be effective in some cases, particularly of the acute variety. ACTH and the corticosteroids were of great help in the initial therapy of a case of hemorrhagic "crisis" with active bleeding from mucous membranes and into the skin. In most cases the beneficial effects appeared to be caused by a nonspecific effect on the capillary wall, as indicated by a reduction in bleeding time and tourniquet test without any concurrent real increase in the platelet level. Usually there was only a transient slight rise in the platelets, but even this effect was inconstant; for this reason we used the corticosteroids only in the acute cases and in the acute crisis of the chronic cases.[16]

With the appearance of the new corticosteroid, prednisone, it seemed desirable to evaluate the effect of this material, especially since large doses could usually be given without causing fluid retention or electrolyte disturbance. It quickly became evident that the administration of prednisone resulted in a striking therapeutic effect on the platelet level, not only in the acute cases, but in the chronic and splenectomized cases as well.[17] Whether this was a dosage effect or due to some specific action of the new steroid molecule was not clear, although the results in occasional cases indicated that it was not a dosage effect alone. This result encouraged us to use prednisone in ITP in much the same manner as we had used this material and the other corticosteroids in AIHA. The results were striking in acute ITP. There was usually a rapid subsidence in the bleeding tendency and a sharp increase in the platelet level. In chronic ITP, results almost as striking were evident in about 60 per cent of the cases, with the platelet counts becoming normal, usually within 2 to 4 weeks. The initial or starting dose was usually 50 to 100 mg. daily, this amount being gradually reduced to 25 mg. and then to lower amounts as the platelet count reached sustained high levels. The dosage was then reduced gradually in the attempt to obtain as low maintenance levels as possible (that is, 5 to 10 mg./day). Many cases relapsed if the dosage was reduced below this amount, but the remission could be reinstated by the further use of a larger dose of prednisone for a short period. In some patients this period of "juggling" dosages was difficult; in others it was simple. In some the drug eventually could be discontinued; in others it was necessary to continue it in small amounts (2.5 to 5.0 mg. day). Occasional cases failed to be benefited, either temporarily or over a long period, and in these, provided hemorrhagic manifestations were present, splenectomy was usually carried out.

We have ascribed the beneficial effects of prednisone in ITP first, to an effect on platelet antibody production, although the evidence for this is relatively scanty in comparison with that in AIHA; second, to a nonspecific effect on the blood vessel wall; or third, to a possible stimulatory effect on platelet production by the megakaryocytes.

An additional reason for our reluctance to remove the spleen in ITP has been the increasing evidence that ITP and systemic lupus are closely related conditions, if not part and parcel of the same disease.[18] Furthermore, splenectomy in apparently typical ITP is occasionally followed in a relatively short time by the development of full-fledged systemic lupus.[19] There is thus some indication that splenectomy removes an inhibiting factor for the development of the disseminated disease, previously present as thrombocytopenia. It is becoming evident that ITP is often merely a prodrome of SLE, and that splenectomy will perhaps make a bad situation of one that was relatively mild.

Thus, since 1950, an actual revolution in the therapy of ITP has taken place in our clinic. Acute ITP is treated by medical measures alone. Chronic ITP, in which we used to recommend splenectomy as a routine measure, is now treated for as long as possible with prednisone in adequate starting amount, then with maintenance therapy, and splenectomy reserved as a measure of last resort. Previously splenectomized ITP in relapse is also treated with prednisone, often with good results. Operation for accessory spleen is no longer done in our clinic; indeed, we consider it to be a wholly useless and perhaps even irrational procedure.

Systemic Lupus

Our views of the autoimmune nature of this disease have been presented previously.[18] We believe that this disorder is a complex of immunological abnormalities involving two systems: the blood and the blood vessels. At some time in the course of the disease the blood may show such abnormalities as AIHA with positive Coombs test, ITP, marked leukopenia and neutropenia with or without leukoagglutinins, a positive L.E. test (probably due to an antinuclear antibody), a positive serologic test for syphilis, and the presence of a hemorrhagic disorder due to the development of inhibitors against thromboplastin or prothrombin. Simultaneously, there is a greater or lesser degree of "vasculitis," that is, immunological involvement of small blood vessels, with the development of conditions such as arthritis, nephritis (glomerulitis), pleuritis, endocarditis, and dermatitis (folliculitis keloidis and other eruptions). The combination of these two kinds of lesions (vascular and hematologic), both of which may well be autoimmune and are possibly caused by the production of several different kinds of antibodies, is called systemic lupus, but it should be realized that the disease may present itself at its inception as a single lesion (for example, ITP); the generalized character of the disease may not become apparent for several years.

In any event, the use of the corticosteroids in SLE has become well established and need not be discussed further here.

Other Immunohematological Disorders

We consider Henoch-Schönlein vascular purpura to be a form of generalized acute vasculitis that is perhaps due to the development of a vascular autoantibody that is active against small blood vessels.[20] The results with large doses of corticosteroid therapy in this disorder are usually striking although, as in systemic lupus, little if any effect on the renal lesion, if present, can be expected.

Thrombohemolytic thrombocytopenic purpura (TTP, thrombotic thrombocytopenic purpura, or Moschowitz disease) is a condition in which there is a more or less simultaneous development of a triad including hemolytic anemia, thrombocytopenia, and generalized small blood vessel thrombosis, with particular involvement of cerebral and coronary blood vessels.[21] Although but little evidence is present for considering this to be an immunological disorder, we believe that it has the various features of such a disturbance, despite the lack of such abnormalities as a positive Coombs test or platelet antibodies. The possibility is present that an acute generalized tissue-reacting (allergic) disturbance has been established. Therapy with ACTH and the corticosteroids has in general been ineffective, although the use of massive dosage has been productive in occasional cases of a complete remission and perhaps eventual cure. If remission occurs, however, the possibility still remains that a chronic, self-perpetuating immunological disorder is present, with flare-ups occurring from time to time. In two cases I have seen, the lupus test eventually became positive, indicating the probably close relationship existing between this disorder and SLE.

To summarize this account of the corticosteroid therapy of immunohematological disorders, it may be said that we have attempted to regard them as a large grouping or system composed of sometimes related, sometimes unrelated conditions, all characterized by injuries to cells or tissues by autoantibodies, and all responding in greater or less degree to the administration of adequate doses of ACTH and the corticosteroids. Whether or not the concept of autoimmunity is accepted, and whether or not the evidence for the presence of autoimmunity in some of these conditions is adequate, there can be little doubt that here is a relatively "new" field of acquired disease in which response to the corticosteroids is one of the important unifying features.

Miscellaneous Disturbances

Aplastic anemia. In this condition, in which the bone marrow has been extensively injured or is congenitally defective, there is striking hypoplasia and hypocellularity of the marrow, with resultant pancytopenia. Since no good marrow-stimulatory substances are available, and since ACTH and the corticosteroids are possibly myelostimulatory, their trial in this disease was justified. Experience indicates that they have their good and bad points. Bleeding due to thrombocytopenia is to some extent alleviated, apparently because of a nonspecific effect on blood vessel wall. Occasional cases show a distinct reticulocytosis followed by an increase in red cells, but this is the exception rather than the rule. In one case occurring in an old man, striking responses in blood counts took place with the use of cortisone and other steroids, but relapse occurred when these compounds were discontinued. This was tried on several different occasions, with identical results. In another case, a 50-year-old woman with total red cell hypoplasia and an otherwise normal marrow ("pure red cell anemia"), the response to the corticosteroids was dramatic; relapse occurred each time the steroid was discontinued. Maintenance therapy of 5 to 10 mg. of prednisone is required in both these exceptional cases. It is apparent that here the material acts as an essential erythropoietic stimulating factor, since no other abnormality appears to be present. The extreme leukopenia and granulocytopenia of some cases are conducive to the development of infections of various types, and when these occur they are apt to be difficult to eradicate. With the use of the steroids, infections tend to become intensified and may pose difficult problems in therapy. To stop steroid might enhance bleeding and prevent the chances for ultimate recovery; to continue with the medication might result in serious and perhaps overwhelming infection. It has been necessary to settle each case on its own merits.

In our recent management of aplastic anemia we have been using the corticosteroids as the first step in therapy, usually in a dosage of 50 to 100 mg. prednisone daily.[22] If a beneficial response takes place, which is unlikely, no other therapy is used. If the response is slight, with perhaps only an amelioration of the bleeding tendency but no effect on the anemia, two other steps in therapy are taken: first, splenectomy, and second, homologous bone marrow transplantation. In some cases splenectomy has been done first, in others marrow transplantation. Our results thus far do not permit any evaluation as to which of these two steps should be carried out first. During these procedures, and without reference to which one is carried out first, the corticosteroid is continued. With the rare exceptions delineated by Medawar,[23] transplantation of homologous tissue, including marrow, is impossible in view of the immunologically mediated "rejection" phenomenon. The use of "lethal" X irradiation to destroy the immunological tissue has been suggested, but our group has taken the stand that this procedure is contraindicated in aplastic anemia where the situation, although bad, is by no means hopeless. Under these circumstances, almost the only materials that might have some effect on the immunological rejection phenomenon are the corticosteroids, which demonstrably have an effect on the first stages of the rejection phenomenon. We have used the corticosteroids routinely for this purpose, usually in the form of large doses of prednisone. Our results have been sufficiently impressive to warrant continuance of these therapeutic efforts.

Fibrinolytic Disturbances

A profound bleeding disturbance may occur when the usually nicely poised fibrinolytic antifibrinolytic balance is disturbed, as in situations such as childbirth, prostatic carcinoma, or operations on the pulmonary tree. Our experience indicates that the use of the corticosteroids in large amounts may be of some benefit in some cases.[24] Usually fibrinogen in large amount is given simultaneously.

General Statements

There can be no doubt that with the introduction of ACTH and the corticosteroids into the clinic, hematological therapy has been revolutionized. It early became apparent, not only with autoimmune hemolytic anemia, but later with acute and chronic leukemia as well, that the dosage essential for a therapeutic effect was usually considerably larger than for such disorders as rheumatoid arthritis. In fact, the dosage required to control a given case of autoimmune hemolytic anemia, for example, might be ten to twenty times as much as to produce comparable effects in rheumatoid arthritis. The necessity of using "pharmacological" dosage was never more apparent than in acute leukemia or in certain cases of ITP. This situation naturally posed the problem of the so-called side reactions: actually undesirable actions in contrast with the desired therapeutic effect. With the development of the delta corticoids, the water-retaining effects of the corticosteroids were drastically reduced, so that massive dosage became possible. However, it was essential to "protect" the gastrointestinal tract by the use of tincture of belladonna before meals and one of the aluminum gels after meals, and to be on the alert for such reactions as psychological disturbances, osteoporosis, infections, and diabetes. Reactions occurred, to be sure, even with all precautions, but their incidence seemed surprisingly small in comparison with the numerous reactions seen with the small doses used in rheumatoid arthritis. It cannot be denied that many of the hematological disorders are, by their very nature, desperate situations. Thus, in order to obtain therapeutic effects in a reasonably short time it has often been necessary to throw caution to the winds and to give massive doses of the corticosteroids. This has often "paid off" in the form of seemingly incredible results.

As for the type of corticosteroid used, we have settled upon prednisone as the best of these agents available to us at the present time. Prednisone has many advantages over cortisone and hydrocortisone, and may be used in large and even massive dosage without very much danger of undesirable reactions. The newer agents, triamcinolone and dexamethasone, appear to offer no particular advantages. In fact, we have discontinued further use of triamcinolone because of its frequent propensity to result in weakness of the quadriceps muscle.[25] The fact that dexamethasone may be given in smaller doses probably carries no particular advantage to the patient. Prednisone has thus remained the standard corticosteroid in our clinic.

Accordingly, over the years the corticosteroids have become the sheet anchor of therapy in many serious hematological cases and the most important of the adjuvant therapeutic principles in others. Faced with the very difficult therapeutic decisions usually seen in the later stages of conditions such as chronic leukemia, lymphosarcoma, Hodgkin's disease, and myelofibrosis with myeloid metaplasia, and after lengthy discussions as to the pros and cons of the alkylating agents, splenectomy, and other means, we have turned more often than not to the corticosteroids as the agents most likely to give the patient comfort and a chance for improvement. The "when in doubt" quality of these remarkable agents has impressed itself on us so forcibly that we now consider use of the corticosteroids seriously in almost all of our cases of serious hematological disturbances.

Summary

When one has read the above account of the beneficial, and at times almost incredible, effects of the corticosteroids in a large variety of hematological dis-

orders, it might appear to the objective observer that the writer of the article was in some manner related to the old-time medicine man who sold in one bottle a concoction guaranteed to cure almost every ill of man and beast. Despite this natural presumption, it must be emphasized that the results presented here only in summary form have been well documented and are based on a large case experience of many diverse hematological problems. It is safe to say that the corticosteroids are often the sheet anchor of hematological therapy, and that their use has to great extent revolutionized the therapy of AIHA and ITP. In our clinic, this has relegated splenectomy for these conditions to a secondary position.

The desperate nature of many of the hematological disturbances, some of them literally matters of life and death, has often led us to throw caution aside and to use doses of the corticosteroids far in excess of those used in other fields. In some cases, as in AIHA, ITP, and acute leukemia, the results of large- or massive-dose corticosteroid therapy, in contrast with small doses, have been very impressive.

Reactions to the large doses used have often been surprisingly few, although there is no question of the necessity for being on the watch for gastric, infectious, osteoporotic, and other complications. In general, the various corticosteroids induce comparable reactions, but triamcinolone seems to result in a higher incidence of quadriceps muscle weakness than do the other materials. Our standard corticoid at this time is prednisone, which we can use in very large dosage and in relative safety.

The introduction of dexamethasone seems to offer no particular advantages over the other corticoids in hematological disturbances.

There is room for further work on the effects of massive ("pharmacological") doses of the corticosteroids on leukocytic proliferations, including those seen in the leukemias and related diseases and on the immunological disorders at the cellular level. Such investigations would be of potential value, not only in the leukemias, but in working out possible dosage schedules for inhibiting the rejection phenomenom in homologous tissue transplantation.

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TREATMENT OF EYE DISORDERS WITH ANTI-INFLAMMATORY STEROIDS

Irving H. Leopold
Department of Ophthalmology, Graduate School of Medicine,
University of Pennsylvania, Philadelphia, Pa.

Investigations of the potential value of cortisone for treating ocular inflammation followed the early and considerable investigations by Wintersteiner and Pfiffner (1935), Mason *et al.* (1940), and Kendall (1940) on the chemistry of steroid substances produced by the adrenal cortex; the demonstration by Sprague *et al.* (1948) and Thorne *et al.* (1949) of the clinical effect upon patients suffering from disorders such as Addison's disease; and the dramatic improvement recorded by Hench *et al.* (1949) in patients with rheumatoid arthritis. Within a relatively short time, some of the most obvious effects on inflammatory process in the eye were established as they had been for other parts of the body (Gordon and McLean, 1950; Woods, 1951; Scheie *et al.*, 1951; Fitzgerald *et al.*, 1951; Lavery *et al.*, 1951; Duke-Elder *et al.*, 1951; Leopold *et al.*, 1951; and Olson *et al.*, 1950). Capillary permeability was decreased; cellular exudation reduced; and granulation-tissue formation, fibroblastic reaction, and the formation of new vessels were inhibited. The steroid also inhibited the ocular inflammatory response to direct organismal infection, to anaphylactic or allergic reactions, and to the injection into the eyes of nonbacterial irritants such as glycerin, jequirity, trimethylamine, colchicine, or talc (Leopold *et al.*, 1951; Biegel, 1951; Woods, 1950; Bourquin, 1950; and Fremann and Overhoff, 1956). It was shown early that cortisone had no bactericidal action and no effect on hypersensitive state in the eye for, although it blocked the inflammatory evidences of an anaphylactic or allergic reaction, once it was withdrawn the ocular tissues reacted in their previous hypersensitive manner if contact with specific antigen was re-established. This was demonstrated by Woods (1950) and by Biegel (1951).

As demonstrated in other tissues, cortisone did not affect the cause of any ocular disease process, but merely provided susceptible tissues with a temporary protection. In Hench's (1950) well-chosen words: "It acts as a fire shield but never puts out the fire nor acts as a carpenter to repair the fire's damage."

The eye is an organ composed of very delicate tissues. Maintenance of optical transparency is a necessity for its function. The inhibition of inflammatory action is an extremely important aim of all ocular therapy. Consequently, steroids have had a large role in the therapeutics of ocular disease, for many of the inflammatory states of the eye cannot be attributed to a specific etiology. In ocular therapeutics with cortisone the aim has been to control the deleterious aspects of the inflammatory response until such time as the infective or other causal agents were eliminated by other methods.

By 1951 it was realized that local cortisone was equal or superior to systemic administration for those tissues with which it could be brought into contact in sufficient concentration to have a therapeutic effect. Generally speaking, this means that local treatment was preferable for diseases of the conjunctiva, sclera, cornea, and the anterior segment of the uveal tract. In diseases of the posterior segment of the eyes, systemic treatment was indicated. This approach thus allowed the use of small quantities of cortisone to control ocular inflammations in the anterior portion of the globe and all but eliminated the adverse systemic side effects that accompany long-continued treatment. By 1951 it had been found that cortisone acetate could be applied in drops, as ointment, and by subconjunctival injection, retrobulbar injection, and injection directly into the anterior chamber. It was also possible, by qualitative testing, to demonstrate the penetration of topically applied solutions, ointments, and subconjunctival injections into the anterior chamber (Leopold *et al.*, 1951).

The frequency of instillation has been determined by the severity of the ocular inflammation. It became obvious, early in the studies, that the therapeutic effect depended upon the severity of the inflammatory process, the size of the dose, and individual susceptibility to the hormone. Small doses, in terms of concentration or frequency of instillation, might only modify the clinical evidences of inflammation while, in the same disease or in the same eye, larger doses might block the inflammation entirely. The remission of the inflammatory action during acute phases is of particular importance in the eye, for it may mean the difference between continued function and blindness. Individuals varied in their response to therapy for similar conditions.

Controls are often difficult to establish in clinical medicine but, in ophthalmology, where bilateral iritis or iridocyclitis has been encountered, it has been possible in some patients to treat one eye with steroid and atropine and the other with atropine alone. It has been reported that the eye that received the steroid showed definitely more rapid resolution than did the other. In bilateral cases where the more severely involved eye was treated with steroid, that eye promptly became the better one. Also, cases have been encountered in which one eye had been lost to a disease similar to one that, affecting the second eye, was controlled by the use of steroid while giving every indication of running an identical course (Duke-Elder *et al.*, 1951).

Experimental studies have been performed with cortisone on tissue reactions and tissue repair in inflammations in the eye. Because an increased permeability of the capillaries was common to all inflammatory processes, the permeability of the normal and the abnormal capillary walls was investigated ophthalmologically. It has been demonstrated by Leopold *et al.* (1951) that there was no significant difference between the rate of appearance of fluorescein in the aqueous humor of normal rabbits without cortisone and the rate of appearance in animals administered cortisone (instilled as drops, injected subconjunctivally, or introduced into the anterior chamber). This finding has been confirmed by the work of Cook and McDonald (1951). Thus, it would appear that cortisone has no significant effect upon the permeability of the normal capillary. It does appear to have a definite effect in restoring to normal a pathologically increased capillary permeability. Cook and McDonald, in 1951, demonstrated that whether administered locally, by instillation of drops or subconjunctival injection, or parenterally, it dramatically reduces the ocular permeability to the normal level from one increased by inflammatory conditions. This reduction of permeability was temporary in that the permeability returned rapidly even though a relapse of the inflammatory symptoms was not clinically evident. It was also demonstrated by Leopold *et al.* (1951) that the increased penetration of an antibiotic such as streptomycin into the ocular tissues and fluids of the inflamed eye could be reduced by the prior administration of a steroid. Streptomycin penetrated to a greater extent into the inflamed eye than it did into the normal eye, and steroids, locally or systemically applied, moved the penetration levels back toward those of the normal eye.

Biegel found that cortisone inhibited the formation of plasmoid aqueous and fibrin deposits in the anterior chamber in rabbit eyes with horse-serum uveitis. This finding has been supplemented by the observations of Ashton and Cook (1951) in their experiments on the healing of incised wounds in rabbits' corneas. Cortisone was found to have a mild but definitely inhibitory effect on the formation of fibrinoid coagulum in the wounds. It is possible that many of the beneficial effects of ACTH and cortisone in the treatment of ocular disease may be attributed to this blockage of the exudative-tissue reaction which, in the eye, may have catastrophic results. There is general agreement in the experimental ocular literature that cortisone inhibits the cellular infiltration associated with inflammation and also the formation of granulation tissue in the healing process in the eye (Woods, 1950, Bourquin, 1951; Biegel, 1951; and Woods and Wood, 1952).

Leopold *et al.* (1951) found that cortisone interfered, although only slightly, with the formation of fibroblast in the corneal stroma of rabbits after experimental wounds, an effect observed by these workers to be less obvious with the topical application of hormone than with subconjunctival injection. These studies suggested that various concentrations of cortisone may have a variable effect on the healing of wounds. Ashton and Cook (1951), confirmed these findings, reporting that the inhibition of fibroblastic activity in the cornea was marked but by no means absolute and related to the amount of cortisone given. With moderate doses, such as normally would be used therapeutically, adequate healing took place, but was less satisfactory than in untreated controls. This experimental observation found its clinical complement, for the literature shows that ocular operations can be conducted with impunity while the patient is under treatment with cortisone (Fink and Beras, 1956; Handl, 1955; and Palmerton, 1955).

There is some evidence that epithelial regeneration of the cornea may be retarded by large doses of steroids, and endothelial regeneration by smaller doses. The dosage for endothelial retardation is in the range of that employed therapeutically (Ashton and Cook, 1951).

There is a general agreement among investigators that cortisone exerts a considerable inhibitory influence on the formation of new vessels during the process of inflammation and repair.

Vascularization of the cornea induced by a variety of stimuli can be inhibited by cortisone. However, the more severe the stimulus, the more cortisone is required for this inhibition; in other words, the activity of the steroid is graded and not absolute (Ashton *et al.*, 1951; Lister and Greaves, 1951; Cook and MacDonald, 1951; and Jones and Meyer, 1950).

Cortisone was introduced into the therapy of ocular diseases approximately eight years ago. Since that time, several related compounds have been prepared, some of which have been tried in ophthalmology. These include, in addition to cortisone acetate and free alcohol, hydrocortisone acetate and free alcohol, 9-alpha-fluorohydrocortisone, hydrocortisone tertiary butyl acetate, prednisone, prednisolone, methylprednisolone, triamcinolone and, most recently, dexamethasone. All of these compounds have antiphlogistic action on ocular tissues. Differences have been reported for various preparations of the same compound as well as of related ones; for example, Gordon and his co-workers (1953) and Hogan *et al.* (1954) believe that the free-alcohol form of hydrocortisone excels the acetate variety for intraocular lesions of the anterior segment. It has been demonstrated also that hydrocortisone acetate is superior as an antiphlogistic agent to cortisone acetate for many external lesions such as vernal conjunctivitis and episcleritis (McDonald and Leopold *et al.*, 1953). This superiority, however, is not as clear for anterior-segment intraocular involvements such as uveitis (Hogan *et al.*, 1954).

Clinical demonstrations have provided evidence that topically applied hydrocortisone is superior to cortisone and that prednisone and prednisolone are superior to hydrocortisone and cortisone in a variety of ocular involvements (Kleberger, 1956; Gordon, 1956; and Turner, 1957).

The effectiveness of the new compounds in controlling intraocular inflammations has been established in rabbits and human subjects and it appears that effects similar to or superior to those of older compounds may be obtained at lower dosage levels (King and Weimer, 1955; O'Rourke *et al.*, 1956; and Gordon, 1956).

Studies have been performed in an effort to determine whether the steroids' ability to penetrate explains some of the differences in apparent clinical effectiveness. The results reveal that modification of the chemical structures of cortisone and hydrocortisone produces compounds that penetrate differently and display variations in anti-inflammatory activity. Furthermore, changing the type of cortisone or hydrocortisone preparation (that is, from the acetate to the free alcohol) contributes to a difference in penetrative ability. Differences in penetration could be demonstrated, but did not seem to be of sufficient degree to account for the differences in anti-inflammatory activity (Weimar and Leopold, 1954; Leopold *et al.*, 1955; and Hamishige and Potts, 1955). It has been shown that a greater concentration of hydrocortisone will be collected in the intact cornea and aqueous humor when hydrocortisone acetate suspension is used than when soluble forms of hydrocortisone phosphate or succinate are used (Fleming and Merrill, 1958). One would anticipate then, on the basis of penetration studies, that the suspension form of hydrocortisone acetate would have a greater antiphlogistic activity than the soluble forms for intraocular involvements of the anterior segment of the globe; clinically, there is some evidence for this.

Penetration studies also indicated that corticosteroids are present in normal aqueous humor (Green and Leopold, 1954) and that their concentration increases following the administration of corticotropin (Lepri and Montanari, 1954).

Attention has been called to the fact that discomfort follows the use of corticosteroid preparations in which the material is in particulate form, and that the soluble varieties or those in which finer particles are in suspension may cause less discomfort (Lippmann, 1957).

Experimental studies have indicated that the reduction of inflammatory response occasioned by cortisone may be disadvantageous in the case of an invading injurious process or agent that could be circumscribed or localized by natural protective reaction (Böke, 1956). This has been demonstrated experimentally and chemically for herpes simplex infections of the cornea (Leopold *et al.*, 1951; Hallett *et al.*, 1951; Ormsby *et al.*, 1951; Thygeson, 1953; Thygeson *et al.*, 1953; and Kimura and Okumato, 1957). Fungus infections have also been increased in virulence by steroids (Ley and Sanders, 1956; Montana and Sery, 1958; and Mitsui and Hanabuse, 1955). This may be the basis for an increase in the severity of *Pseudomonas* ulcers of the cornea observed in rabbits when cortisone was administered (Suie and Taylor, 1956; and Mitsui and Hanabuse, 1955).

The value of cortisone and related substances in the treatment of nonbacterial and nonviral inflammatory diseases of the eye has been well established (Bohringer, 1956; Duke-Elder and Goldsmith, 1955; and Leopold, 1956).

A comprehensive review of the available literature on the use of steroids in ophthalmology allows a number of conclusions to be drawn. These include the fact that application of corticosteroids to the anterior segment of the eye is without benefit in inflammatory conditions of the posterior segment. When systemic administration is required, corticosteroids are more convenient than corticotropin because of the ease of oral administration but, in some instances of particularly severe inflammation of the posterior segment, corticotrophin may prove to be more effective. Corticotropin has the advantage of a prolonged action and does not suppress the adrenal cortex, but the adrenal cortex must be able to respond in order for this agent to be effective. Systemic therapy with either corticosteroids or corticotropin is contraindicated in the presence of diseases such as tuberculosis, peptic ulcer, severe hypertension, cardiac disease, diabetes, or an acute infection for which there is no specific treatment.

The many contraindications to the use of systemic corticosteroids or corticotropin are well covered in other presentations in this monograph, and are equally applicable to ophthalmological management.

There are many advantages to the local use of cortisone: there is little danger of systemic reaction, the cost to the patient is less, hospitalization is not necessary, and local treatment probably can continue almost indefinitely. No deleterious systemic effects have been reported from continuous local therapy, and high local concentrations can be utilized. However, clinical and experimental studies have demonstrated no great advantage to the employment of massive doses locally administered (Leopold, 1951).

Topical and systemic therapy with corticosteroids and the parenteral use of corticotropin can give favorable results in such external ocular inflammations as contact dermatitis, rosacea keratoconjunctivitis, allergic conjunctivitis, marginal corneal ulcers, phylectenulosis, and allergic keratoconjunctivitis. The treatment may be of some benefit in nodular episcleritis and pemphigus. Therapeutic effect is unreliable and variable in external conditions such as episcleritis, rheumatic nodules, and collagen diseases of the eye. Temporary regression and thyrotropic exophthalmos and pseudotumor of the orbits have been reported.

Nongranulomatous iridocyclitis and posterior nongranulomatous uveitis respond most favorably to the steroids. The therapeutic response of iritis to topical therapy and of posterior nongranulomatous uveitis to systemic therapy is prompt. If the treatment is continued throughout the natural life of the inflammation, results simulate a cure. In dealing with sympathetic ophthalmia, corticotropin administered by intravenous drip and followed by oral and local steroids is the best treatment yet developed. It may be necessary to continue therapy for many months or years, gradually tapering it off until the eye remains quiet without further treatment. Recurrences of inflammation are encountered, but usually subside with increased dosage and frequency of administration of the steroids. Intensive hormonal therapy is indicated in ocular sarcoidosis, but recurrences still occur when treatment has been stopped. Sometimes the recurrences are kept under control or prevented by continued use of local steroids and the intermittent use of systemic ones.

There are many disadvantages to the use of steroids. Intraocular pressure is usually affected favorably or not at all by the use of steroids (Crawford, 1951). However, an increase in ocular tension during local treatment of uveitis with cortisone has been reported (Francois, 1954). A more serious elevation in tension was reported to follow the administration of corticotropin in patients with uveitis (Laval and Collier, 1955). In addition, local and systemic steroid therapy appears to accelerate dendritic keratitis and fungus infections of the conjunctiva and cornea, and apparently may enhance the chances for the development of pyocyaneous infections of the cornea. Steroids should not be used in bacterial infections where specific antibiotics or chemotherapeutic agents cannot be employed. There is some question of the value of steroids in the treatment of intraocular hemorrhages.

Summary

It is evident from the study of the literature that steroids such as cortisone have no effect on the permeability of the normal capillaries, but significantly lessen the increased permeability characteristic of inflammation, and that the exudative phenomena associated with inflammation are inhibited. It is clear that cellular infiltration and formation of granulation tissue are also retarded and that fibroblastic proliferation of wound repair, as well as vascular invasion of the cornea, are slowed by the use of these hormonal agents. Endothelial regeneration may be impaired by steroids in the usual dosage, but epithelial regeneration requires large doses for impairment.

Penetration studies reveal a difference in the degree by which these agents are able to penetrate through the cornea when locally applied, but this cannot be correlated directly with antiphlogistic activity. There is also a difference in penetration from the blood stream into the eye, but this greater penetration similarly cannot be correlated with anti-inflammatory effect in the eye.

In addition to the well-known side effects and contraindications to the use of steroids by the systemic route, these compounds should not be used in cases that may be harboring, or are predisposed to herpes simplex keratitis, a variety of fungal infections, or in cases of bacterial infections for which specific antibiotic or chemotherapeutic measures have not been employed or are not available.

Local steroids are valuable for anterior-segment inflammation. Systemic steroids or systemic corticotropin are helpful in posterior-segment inflammation. Local steroids have definite, obvious advantages over the systemic routes of administration for anterior-segment inflammation.

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THERAPEUTIC AND SIDE EFFECTS OF THE ANTI-INFLAMMATORY STEROIDS ON THE GASTROINTESTINAL TRACT*

Walter L. Palmer and Joseph B. Kirsner
Department of Medicine, University of Chicago, Chicago, Ill.

The question of the therapeutic and the side effects of the anti-inflammatory steroids on the gastrointestinal tract has been and continues to be controversial. The most important of the alleged side effects is peptic ulcer. The literature contains a multitude of case reports describing in detail the production or reactivation of such lesions in conjunction with the administration of steroids. Some express the view that there is a definite cause-and-effect relationship; others consider it to be simply coincidence.

The frequency of peptic ulcer is not known precisely. Statistics vary for different geographic areas, for different age groups, and according to the methods used for computation. Autopsy figures, not uniform in themselves, are not to be compared with clinical estimates or with roentgenologic reports. Symptoms of dyspepsia are not synonymous with peptic ulcer, and roentgenologic diagnoses are often matters of interpretation. A massive hemorrhage or an acute perforation of a peptic ulcer usually results in a definite diagnosis. The temptation to relate such an episode to some previous event or medication is almost irresistible, even if one bears in mind the old fallacy, *post hoc, ergo propter hoc.*

With respect to the steroids,[1] there are several problems to consider.

(1) Is the incidence of ulcer greater than is to be expected?

(2) Are certain age, disease, or population groups more susceptible to the development of ulcer than other groups?

(3) Is there any difference between the ulcerogenic effects of the various steroids?

(4) If such an effect is present, what is its mechanism?

Perhaps the first of these questions is the most crucial. Kern *et al.*[2] used as a reference base the work of Doll and Jones[3] in England, estimating the incidence of ulcer in men to be 5.8 per cent; in women, 1.9 per cent. Henderson[4] apparently accepted an over-all figure of 6 per cent. Eusterman and Balfour,[5] observing approximately 16,000 patients with digestive disturbances, reported roentgenologic evidence of duodenal ulcer, active or healed, in 12.2 per cent, plus an additional 1.0 per cent for gastric ulcer. Robertson and Hargis[6] found active or healed ulcer in 12 per cent of 2000 routine post-mortem examinations. Which of these figures shall we accept as control values for patients undergoing therapy? Valid objections can be raised to the use of any; hence, it is difficult to find a satisfactory "normal" incidence of peptic ulcer.

Kern and his associates[2] compared patients with rheumatoid arthritis receiving a small dose of cortisone or prednisone with those receiving a large dose (TABLE 1). They found 1 new ulcer and 1 exacerbation of an old ulcer in the

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116 patients in the low-dose group, as compared with 5 new ulcers and 2 exacerbations in 22 patients in the high-dose group. Statistically, this difference is highly significant except for the fact that both groups are small, especially the high-dose group. Altogether, there were 9 ulcers in 138 patients, an incidence of 6.5 per cent. This is close to the 6.0 per cent incidence estimated by Doll and Jones[3] and by Henderson,[4] and obviously lower than the 10 to 12 per cent figures previously mentioned. However, when Kern and his associates compared their data with the expected rate calculated by Doll and Jones, they obtained a ratio of actual to expected ulcer in men of 19:1, and in women of 27:1 (TABLE 2). This comparison cannot be accepted as valid, for there are too many variables, both known and unknown, such as the use of other potentially ulcerogenic drugs in the rheumatoid group. Avery Jones[7] reports that duodenal ulcer is commoner in north England than in south England, that agricultural workers are least liable to ulcer, and that nonsmokers have a substantially lower incidence of ulcers than smokers. Even altitude has been shown by Garrido-Klinge and Pena[8] to have a definite influence, gastric ulcer particularly being more common in high altitudes. Hence, the adult population in England cannot be accepted as a satisfactory control for rheumatoid patients in Colorado.

TABLE 1

RELATIONSHIP BETWEEN THE DOSE OF ADRENOCORTICAL HORMONES AND PEPTIC ULCERATION*

Dose	Patients	New ulcers	Exacerbation	Total ulcers	Percentages
Small	116	1	1	2	2.0
Large	22	5	2	7	32.0
Total	138	6	3	9	6.5

* From Kern *et al.*[2]

TABLE 2

INFLUENCE OF RHEUMATOID ARTHRITIS THERAPY ON THE PROBABILITY OF DEVELOPING PEPTIC ULCER*

Treatment	Sex	No. of patients	No. of man-years treated†	No. of ulcers expected	Actual No. of ulcers	Ratio of actual to expected ulcers
Adrenal steroid	M	43	47	0.153	3	19:1
Adrenal steroid	F	77	88	0.144	4	27:1
Phenylbutazone	M	40	28.7	0.093	2	21:1
Phenylbutazone	F	67	51.5	0.084	5	59:1

* From Kern *et al.*[2]

† Although the number of man-years in each group is small, the ratio of actual to expected ulcer is similar in each instance.

A very recent study by Meltzer *et al.*[9] included 2 groups: 55 patients who had been on long-term steroid therapy and 60 who were examined both before and after such therapy. The incidence of ulcer in the first group was 10.9 per cent and, in the second, 10 per cent, with no new ulcers developing during treatment (TABLE 3). This work gives us, then, a control group with an incidence of ulcer as high as that found in the treated group and, indeed, somewhat higher than that described by Kern *et al.* Thus, again, we have no evidence of an increased incidence of ulcer in rheumatoid patients receiving steroids.

The second question—that is, the susceptibility of different population groups to peptic ulcer—has been answered partially. In studying the incidence of new ulcer in patients who had had arthritis less than 10 years, Kern *et al.*[2] found 6 in 108 patients (5.5 per cent), and an incidence of 9 in 61 (14.7 per cent) in patients who had had arthritis more than 10 years: a difference which did not "quite reach statistical significance" (TABLE 4). Addition of the two groups gives 15 new ulcers in 169 patients (9.0 per cent). The Meltzer[9] findings were slightly higher (10 per cent) before and after treatment. Both figures are lower than those of Eusterman and Balfour[5] obtained in patients screened for digestive disorders. This is a very incomplete answer to the question of the natural susceptibility to ulcer of the various population groups, especially those receiving steroid therapy, but perhaps it is enough to suggest that the data available are very inconclusive.

TABLE 3
INCIDENCE OF ULCER IN PATIENTS TREATED WITH PREDNISONE*

Group		No. of patients	No. of ulcers†	Percentages
I	After steroid therapy	55	6	10.9
II	Before steroid therapy	60	6	10.0
II	After steroid therapy	60	6	10.0

* From Meltzer *et al.*[9]
† Healed or active.

TABLE 4
RELATIONSHIP BETWEEN DURATION OF RHEUMATOID ARTHRITIS AND PEPTIC ULCER*

Duration	No. of patients	No. of ulcers	Percentages
Less than 10 years	108	6	5.5
Ten years or more	61	9	14.7
Total	169	15	9.0

* From Kern *et al.*[2]

In view of these difficulties, it is futile to discuss the third question: the alleged differences in the ulcerogenic action of the various steroids; likewise, the fourth question—the hypothetical mechanism of action—is not in order, although it may be appropriate to mention that one of us has found the gastric secretory output unchanged even after weeks, months and, in two patients with ulcerative colitis, more than one year of continuous hormonal therapy.

Perhaps at this point reference should be made to the fact that since 1950 we have treated more than 240 patients with chronic ulcerative colitis with large amounts of steroid[10] (TABLE 5). At least 9 patients had histories of peptic ulcer prior to therapy and were found roentgenologically to have bulbar deformity. In no instance did activation of the ulcer occur during therapy. One patient, prior to coming to us, had an ulcer with massive hemorrhage during prednisone therapy. One of our young female patients with scleroderma and ulcerative colitis developed a bleeding duodenal ulcer while receiving 400 mg. of cortisone daily; at the same time, however, another young female with ulcerative colitis who was not receiving steroid therapy also developed a bleeding duodenal ulcer. One patient without ulcerative colitis but with advanced rheumatoid arthritis and amyloidosis developed an ulcer while on cortisone. A young man who survived colectomy and ileostomy developed a "massive necrotizing inflammation" of the stomach with 3 ulcers, hemorrhage, and perforation while receiving prednisone. This patient may be matched, as it were, by a man with ulcerative colitis and an ileostomy who died from a similar gastric perforation in 1949, prior to the introduction of cortisone. Thus, in the pressure of clinical practice, accurate differentiation between causality and chance is difficult. It is also of interest that Goldgraber, in a review of 70 patients who had received steroid therapy for idiopathic steatorrhea, did not find any mention of peptic ulcer as a complication.

TABLE 5
INCIDENCE OF ULCER IN 240 PATIENTS WITH ULCERATIVE COLITIS TREATED WITH STEROIDS

	No. of patients
History of ulcer, with X-ray evidence of deformity	9 (No recurrence during steroid therapy)
Ulcer developed during therapy	2

In summary, then, the evidence does not seem to warrant the conclusion that peptic ulcer occurs excessively in patients with rheumatoid disease or in those receiving the anti-inflammatory steroids.

This paper has been devoted thus far to the alleged ulcerogenic side effects; we now propose to discuss briefly the therapeutic value of the steroids. In general, steroids are "nonspecific" remedies for "nonspecific" diseases of the gastrointestinal tract. This statement is an oversimplification and suggests quite inadequately the therapeutic value of steroids.

There is much confusion concerning the various forms of steatorrhea, or the malabsorption syndromes, including idiopathic steatorrhea, nontropical and tropical sprue, Whipple's disease, and coeliac disease. The pathology has been clarified greatly by the recently introduced biopsy methods. From the standpoint of etiology, some of these disorders are related to gluten in the diet (so-called gluten-induced enteropathies), and are dramatically relieved by gluten-free diets. The anti-inflammatory steroids are almost as effective therapeutically; in some instances, more effective. The increased absorption of foodstuffs in the intestines during such therapy has been carefully documented[11] (FIGURE 1).

Regional enteritis and chronic ulcerative colitis are presumably independent diseases, but they have much in common; they affect the gut, they have no known etiology, they produce inflammation and ulceration, and they are influenced favorably in the majority of instances by the anti-inflammatory steroids. Our experience has been much greater with ulcerative colitis than with regional enteritis. In 1958 we presented an evaluation of 8 years of study[10] (TABLES 6 and 7). In therapy, we have made use of every procedure that we considered valuable rather than using steroids alone. On the other hand, steroids have been an important cornerstone of therapy, and the dosages have been large (TABLES 8 and 9). It is necessary to give enough steroid to control the symptoms completely, and then to reduce the dose very slowly, as indicated by careful observance of the symptoms (FIGURE 2). The manner in which the severity of the disease can be titrated against the amount of steroid required to control the symptoms is one of the most fascinating aspects of the subject. Adequate steroid therapy controls the fever, if present, improves the sense of well-being and the appetite, decreases the number of bowel movements, increases the absorption of water, improves the consistency of the feces, controls the bleeding, decreases the friability and granularity of the mucosa as seen

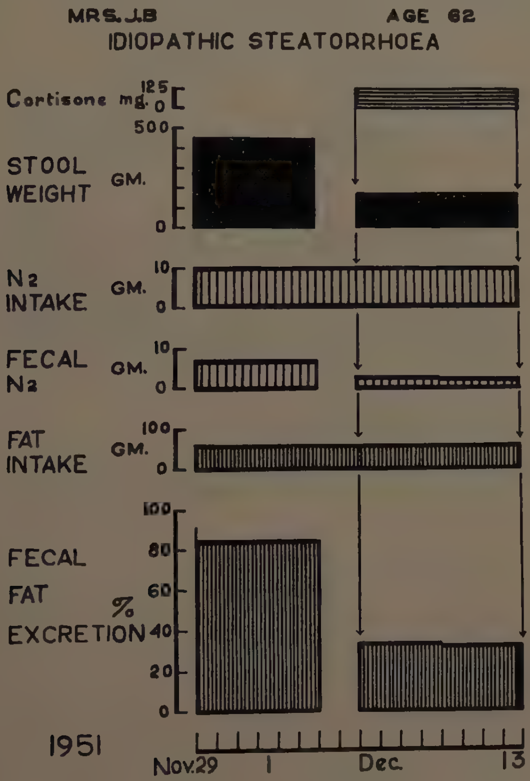

FIGURE 1. Effect of cortisone on fecal weight, nitrogen, and fat (Finlay and Wightman[11]).

TABLE 6

SEVERITY OF ULCERATIVE COLITIS*

Mild†	12
Moderate	86
Severe	142
Total	240

* Data compiled from clinical, proctoscopic, and radiological data.

† Limited roentgen involvement; persistent disease clinically.

TABLE 7

ADDITIONAL INDICES OF SEVERITY OF ULCERATIVE COLITIS

Index	No. patients
Colectomy recommended previously	100
Blood transfusions	104
Previous ACTH, steroids	88
Intensive psychotherapy, psychoanalysis	12

TABLE 8

DOSAGES OF ACTH AND OTHER STEROIDS IN ULCERATIVE COLITIS

Compound	Approximate daily dosage*	
	Initial	Maintenance
ACTH	I.M. 120–160 U. I.V. 20–40 U.	20–80 U.
Cortisone	300 mg.	60–80 mg.
Hydrocortisone	200 mg.	40–80 mg.
Prednisone, prednisolone	40–60 mg.	15–30 mg.

* Individual variation.

TABLE 9

DISTRIBUTION OF ACTH AND OTHER STEROIDS IN ULCERATIVE COLITIS

Compound	No. of patients
ACTH alone	67
Cortisone	8
Hydrocortisone	17
Prednisone, prednisolone	29
Combinations of oral steroids	20
ACTH, oral steroids*	99
Total	240

* ACTH given first, then replaced by steroid.

through the proctosigmoidoscope, and facilitates healing of the bowel. Roentgenologic evidence of improvement occurs much more slowly; indeed, only after months or years. The desired goal of therapy is a patient who looks and feels well, who eats with relish a somewhat limited diet, who defecates formed stools without blood, and whose rectal mucosa appears normal through the proctoscope (TABLES 10 and 11). Failures occur even with maximum therapy. The explanation of the failures, like the explanation of the disease itself, is not

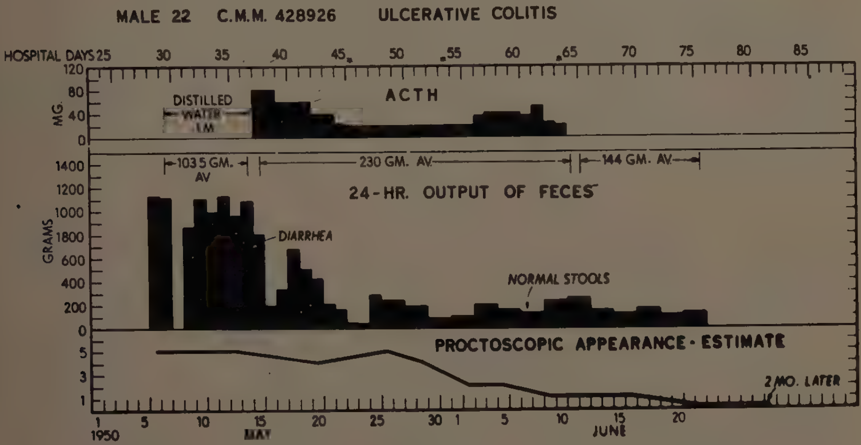

FIGURE 2. Effect of corticotropin on fecal output and proctoscopic appearance of the mucosa. Note preliminary control period.[14]

TABLE 10

CLINICAL RESPONSE TO COMBINED MEDICAL STEROID TREATMENT

Response	No. of patients
Good	115
Moderately favorable	80
Slight or nil*	45
Total	240

* Favorable response initially in 20 patients.

TABLE 11

PRESENT THERAPEUTIC STATUS OF 243 PATIENTS

Steroids continued	101
Steroids discontinued	99
Patients operated (living)*	20
Patients operated (deceased)	6
"Medical" deaths	17
Total	243

* Three still receiving steroids.

manifest unless one is content with the statement that there seems to be a degree and extent of ulceration too great for the reparative processes to overcome. The best indication that this end point has been reached seems to be

TABLE 12

IMPORTANT SIDE EFFECTS OF STEROID THERAPY IN ULCERATIVE COLITIS*

Side effects	
Emotional problems	
Increased	22
Psychosis	15
Suicide	3
Diabetes	6
Hyperglycemia, glycosuria	30
Infections	43
Hypertension	45
Severe hypercorticism	35
Serious electrolyte disturbance	15
Osteoporosis	6
Possible allergy to ACTH	9
Alleged side effects	
Peptic ulcer (X ray positive)	2
Minimal melena and symptoms (X ray negative)	2
Perforation of colon	2

* Excluding "usual" hypercorticism

TABLE 13

FREQUENCY OF PERFORATION IN ULCERATIVE COLITIS IN PRESTEROID ERA

Authors	Year	No. of patients	Perforation	Frequency, %
Bargen, Jacobs	1929	647	22	3.4
Hurst	1935	100	1	1.0
Hurst (Guy's Hospital 1888–1907)	1935	55	6	11.0
Feder	1938	88	3	3.4
Jankelson *et al.*	1945	145	11	7.0
Ricketts, Palmer	1946	206	7	3.4
Warren, Sommers	1949	180	14	7.7
Rice-Oxley, Truelove	1950	129	4	3.1
Brown, Kasich, Weingarten	1951	147	23	15.6

the inability of the bowel and the patient to respond clinically to adequate steroid therapy.

The clinical manifestations of hypercorticoidism are familiar to everyone (TABLE 12). Many of them can be controlled by restriction of salt and calories, by the use of sedative and tranquillizing drugs, by psychotherapy, and by other means. We have had our share of difficulties and are under no illusions with respect to the hazards involved. These must be balanced, however, against the good accomplished.

Perforation of the colon, one of the alleged side effects of steroid medication in ulcerative colitis, is a complication of the disease and, indeed, was more common in the presteroid era[12] (TABLE 13). Goldgraber, studying our material, found 10 fatal perforations of the colon in 400 patients with ulcerative colitis between 1930 and 1949; in 240 patients treated with steroids from 1950 to 1957, inclusive, there were 2 such fatal perforations. A careful analysis of the symptoms in the 2 groups revealed no difference; "masked perforation" occurred before as well as after the introduction of corticoid therapy and giant "shaggy" ulcerations were encountered in both periods. It will be recalled that, in the therapeutic trial of cortisone in ulcerative colitis supervised so excellently by Truelove and Witts[13] in England with a splendid control series, 2 perforations of the bowel occurred in the control group and none in the treated group.

TABLE 14

FATAL PERFORATION OF THE COLON IN CHRONIC ULCERATIVE COLITIS

	Patients	Fatalities	Percentages
Presteroid era (1930–1949)	400	10	2.5
Steroid era (1950–1957, inclusive)	240	2	0.84

Conclusions

The alleged ulcerogenic effect of the anti-inflammatory steroids must be considered unproved.

The beneficial therapeutic effects of the adrenal steroids as nonspecific agents in the nonspecific inflammatory diseases of the small and large intestine are established.

At the present time, lesions of the gastrointestinal tract cannot be included in the complications of steroid therapy.

Acknowledgment

We are grateful to the following for their generosity in supplying steroid hormones: Wilson & Co., Chicago, Ill.; The Upjohn Company, Kalamazoo, Mich.; and Schering Corporation, Bloomfield, N. J. Moshe Goldgraber has been most helpful in providing data.

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TREATMENT OF NEPHROSIS WITH ANTI-INFLAMMATORY STEROIDS

Conrad M. Riley

Babies Hospital and Columbia University College of Physicians and Surgeons, New York, N. Y.

Anyone who has had a special interest in nephrosis for 10 years or more will find it easy to call to mind the clinical picture of this affliction in the presteroid days and to contrast it with what we see now. In preparation for this presentation, as I reviewed some of the many reports of the past 8 to 9 years, I discovered that the transition was not as easy or as abrupt as unaided memory would suggest. It is also interesting to see that, with the use of these new, primarily therapeutic tools and with new developments in allied fields, the concept of nephrosis as a distinct disease entity has grown a little firmer. Therefore, recapitulating the somewhat devious route we have been following seems a worthwhile endeavor.

Although 1948 was the year in which the artificial induction of the hyperadrenocortical state was first shown to be capable of altering some types of human disease, it was only at the end of that year that Edith Farnsworth of Chicago, Ill.,[1] requested a supply of corticotropin for use in nephrosis. Early in 1949 she began clinical trials in this and other renal disease, so that she was able to report some effect at the first ACTH conference in October of that year.[2] Even before her report, others of us had begun to try it in a few cases. When one considers, in the light of present practice, the duration of treatment and the size of the doses given in some of the early trials, it seems a stroke of good fortune that results were sufficiently impressive to justify further exploration of this form of therapy.

In May of 1950 at the spring scientific meetings, reports (later published) were submitted by Luetscher,[3] Barnett,[4] and myself[5] showing the clinical and metabolic effects of both cortisone and corticotropin on patients with the nephrotic syndrome. By this time it was established beyond doubt that such treatment with adrenocortical-active hormones was quite regularly associated with remission; there was some evidence of improvement in renal function, but much doubt was expressed as to whether the basic disease process was altered significantly. It is of historic interest that at that time, before aldosterone had been identified, Luetscher[3] was able to show by bioassay an excess of "sodium-retaining corticoids" (which disappeared with diuresis) in the urine of nephrotic patients. Review of my own balance data on a patient with induced diuresis shows that the Na:K ratio increases with diuresis, indicating diminished aldosterone activity, an interpretation not appreciated at the time. Thus there was both direct and indirect evidence for the role, probably secondary, played by aldosterone in nephrosis. Such information justified these drugs as an investigative tool, since they made diuresis an almost predictable possibility.

In these early days the methods of giving adrenocortical-active medication showed far more fear of harmful effects than conviction that a valuable new group of therapeutic agents had been discovered. In this brief backward glance, no effort to cite all of the pertinent references has been made. Instead, in an attempt to touch only on the most significant developments, we have relied upon memory refreshed by the *Proceedings of the Annual Conference on the Nephrotic Syndrome*, published regularly, beginning in 1951,[6] when the third such conference was held. In the discussion of therapy at these meetings, recorded verbatim, there can be seen all the enthusiasm and skepticism that might be expected to accompany the advent of a new and highly potent agent.

In the 1951 conference, several of the discussants, including myself, were quoted as saying that the new treatment should be held in reserve until the patient was so uncomfortable or the parents so insistent that the use of something so radical seemed justified. It was in that year, however, that Kurt Lange pointed out the fluctuations of serum complement correlated with remissions and exacerbations.[6] His data suggested that after a period of ACTH administration there was a sudden rise in the level of serum complement, followed immediately by diuresis. If no further treatment was given, the complement level tended to fall, but if ACTH was given for three consecutive days each week, this fall was apparently checked, and the patient had a period of remission longer than might have been expected. This was the earliest suggestion that treatment should be given even when the patient was in clinical remission.

From that era to the present there has been a gradual evolution of answers to these three questions on the treatment of nephrosis: (1) What plan of hormone administration is most effective? (2) What does such treatment actually accomplish? (3) What pharmacological preparation is the most effective? Although the developments in all the areas involved were closely interrelated, for simplicity of discussion each question will be considered separately.

First, the steroids (a term used inaccurately for brevity to include both adrenocorticotropin and adrenal glucocorticoids) were given in relatively small doses for from 4 to 10 days; it seemed in 1951 and 1952 that 60 to 80 per cent of such courses could be counted on to induce at least temporary remission. By the fall of 1953, at the Annual Conference on the Nephrotic Syndrome, much more thought was given to treatment of the patient even in the absence of symptoms. In addition to Lange's 3-day-a-week schedule, Lawrence Greenman and T. S. Danowski of Pittsburgh, Pa., reported 28-day continuous steroid administration, well beyond the time when diuresis occurred, with greatly prolonged remissions. Benjamin Kramer of Brooklyn, N. Y., reported two 10-day courses in rapid succession. In the 1954 conference, even more extended periods of hormone administration were discussed by Arthur Merrill of Atlanta, Ga., and Harriet Guild of Baltimore, Md.

Without attempting to enumerate all the different ways of administering these hormones, we shall move on to a generalization about current practice. Although anyone caring for large numbers of patients has his own plan of management, it is fair to say that all of us follow these general principles.

(1) Treatment is started with large doses of adrenocortical-active hormones as soon after diagnosis as possible.

(2) Continuous treatment is given beyond the point of symptomatic relief until all measurable abnormalities have returned to nearly normal.

(3) Repeated treatment is planned to be given either arbitrarily, on a fixed

time schedule, or on minimum laboratory evidence of relapse. Underlying this is the strong conviction that symptomatic treatment is not enough.

Second, with respect to the actual results of treatment, there has been a great change over the years. Early conference proceedings[6] showed a great feeling of doubt that such therapy was giving anything more than symptomatic relief. Indeed, the early figures based on the short courses that were given only to relieve symptoms showed no significant changes in survival rates. By 1955, however, as a result of a cooperative study, it was possible to show fairly convincingly that "intensively treated" patients had a significantly better survival curve than those without treatment or with only symptomatic treatment. The most recent cooperative study[7] shows a highly significant improvement in survival, after 4 years of disease, among patients whose disease began sufficiently recently to have had the chance of intensive steroid treatment as compared with those whose disease began before steroids were available. In FIGURE 1 are shown 2 survival curves, *B*, the control, based on patients whose illness began in the presteroid era, and curve *A*, based on those whose illness

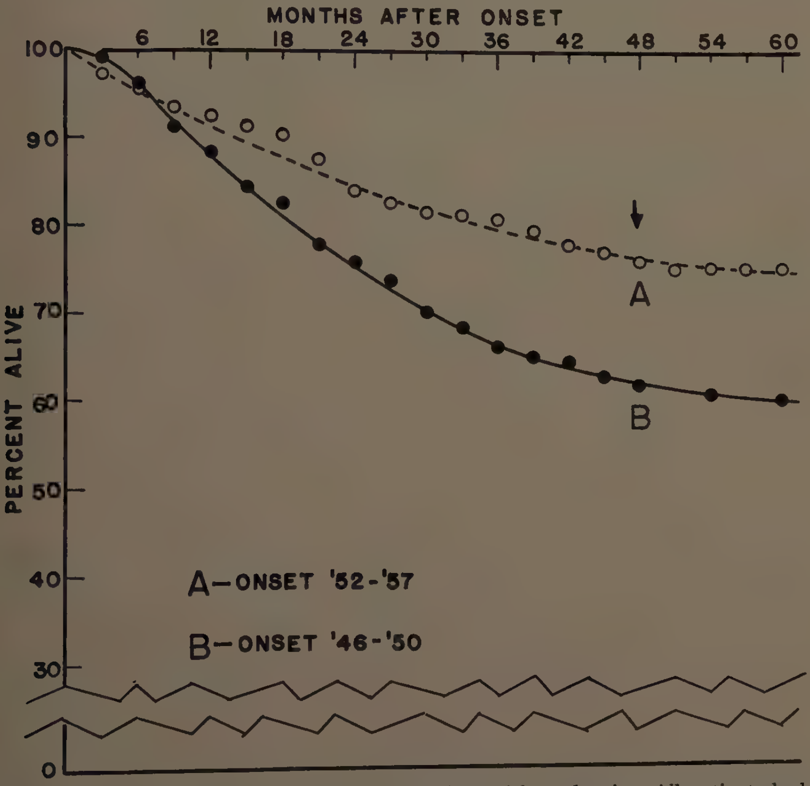

FIGURE 1. Survival curves of 2 groups of children with nephrosis. All patients had an onset of disease in the years indicated, were under observation within the first 6 months after onset, and were less than 12 years old at onset. Curve A is based on 554 cases, and Curve B on 338 cases. Data from Riley and Scaglione.[7]

began more recently. The pooling of figures from many clinics made groups sufficiently large to prove the highly significant difference in survival 4 years after onset. It may be seen that only 60 per cent of the early groups were still living at this point, whereas more than 75 per cent of those in the current series have survived. There is no reasonable doubt that life is being prolonged by modern treatment.

There is additional evidence to show that the basic disease process is being suppressed. It has long been known that with successful steroid therapy all measurable chemical abnormalities (proteinuria, hypoproteinemia, hyperlipemia) return to normal. Galan[8] has demonstrated improvement in the histological aspects, with the usual techniques, in serial renal biopsies. Piel[9] and Vernier[10] more recently demonstrated a return to normal, following treatment, of changes demonstrated by the electron microscope. In addition to this we have the impression, shared by others, that the proportion of patients developing signs of renal failure has diminished significantly. Thus, all available evidence suggests a true suppression of the basic disease process. This suppression can be maintained for long periods and, in many instances, spontaneous healing occurs, so that the need for therapy disappears. It should be emphasized, however, that steroid therapy for nephrosis is a suppressive measure, not a curative one.

Finally, as for the question as to which of the many agents of the adrenocortical-active group is most effective: for reasons of availability, corticotropin was most widely used in the early part of this decade. Many investigators felt it was superior to the anti-inflammatory steroids, and some still do. It has been our feeling that, when it has appeared to be more effective, the better results could be explained by its being better absorbed from an intramuscular route of administration than from an edematous gut.

Very early, following Luetscher's example,[3] we shifted to cortisone administered either by mouth or by injection, and could see results not noticeably different from those achieved with corticotropin. When the delta-1 drugs (prednisone and prednisolone) became available, their diminished salt and water retention property became so evident that the parents themselves protested the suggestion of returning to the cortisone-hydrocortisone type of drug. This salt-retaining effect may readily explain the early observation that diuresis often was associated with withdrawal of the drug. If one assumes that the drug was producing a basic alteration of the disease process, such as a diminished leakage of protein through the glomeruli, but simultaneously was causing an increased degree of sodium retention, then withdrawal of the drug and cessation of the latter action would allow immediate diuresis. Nowadays, however, when the delta-1 derivatives with little or no salt-retaining effect are used and when periods of administration are longer, diuresis during treatment is the rule.

Other new steroid preparations have been introduced. These include triamcinolone, 6-methylprednisolone, and most recently, dexamethasone. Clinical experience with any of these is too short to make comparative statements as to their merits. Milligram doses vary considerably with any of these, but there is no convincing evidence that the undesirable effects are decreased any more by diminished doses than are the desirable effects. In other words, if one uses therapeutically equivalent amounts of these newer preparations, it is likely that he will experience similar undesirable side effects. It is noteworthy that, although occasional tragic complications have developed in association with steroid therapy, this has not been a major problem in treatment of children. I have not been able to titrate the potency of steroids in patients with nephrosis because the observable response is so delayed. On the other hand, I have accepted dose equivalence as reported by those using drugs for an easily titratable condition such as rheumatoid arthritis, where the end point is clear. Using such standards, I have found that transition from one agent to another has been easy and the results reasonably predictable.

Summary

The method of administering steroids for treatment of nephrosis has changed greatly. The short, small-dose courses have been superseded by fairly long periods of large doses followed by several periods of further treatment for months or years, even in the absence of symptomatic disease. The fear of undesirable effects, although not forgotten, has been dwarfed by the recognition of proved suppression of a potentially lethal disease, which makes the recognized risks justifiable. The still unsettled question is which of the many agents is the most useful. The analogue that causes least salt retention is to be desired but, because of the long periods involved in the response of nephrotic patients to treatment, this disease would not appear to be the one on which to test this property.

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Discussion of the Paper

Question: Is there any correlation between the renal biopsy and the response to therapy—in other words, the histological picture? Second, can Riley tell us whether he routinely uses antibiotics in conjunction with steroid therapy? If so, can he tell us what part antibiotics play in the control of this condition?

CONRAD M. RILEY: The renal biopsy and its relation to treatment is a relatively new development, but there has been some early work both with the light microscope and with the electron microscope. After a clinical remission, there is improvement of any pathological changes that may have been observed by the light microscope. In cases where pathological changes can be observed only by electron microscope, a clearing of these changes also occurs when a good remission is induced by steroids.

The question of antibiotics is an interesting one. From the over-all point of view, is the difference in mortality rate between the older group and the present group causally related to antibiotic therapy? The patients in the control group consisted of those whose disease started after 1946, when the antibacterial agents then available had already reduced deaths from infection by a large degree. In our steroid-treated group of patients death from infection has remained in about the same proportion as in the earlier nonsteroid group between 1946 and 1950, although the proportion of deaths due to renal failure has markedly diminished in the current as compared with the earlier group. Therefore, I do not think that antibiotics are responsible for the difference in the over-all mortality rate between the older and the present groups.

We do, of course, use antibacterial preparations when we administer the steroids. I wonder if this is superstition remaining from the days when we felt that the steroids had a great capacity for predisposing to infection. I know that there are many who do not employ antibacterial agents when they give the steroids and yet who do not seem to be experiencing any more trouble than we do. Our use of antibiotics may be due more to superstition than to actual need.

TREATMENT OF PULMONARY EMPHYSEMA AND COR PULMONALE WITH ANTI-INFLAMMATORY STEROIDS

Alvan L. Barach and Eduardo R. Pons, Jr.
Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y.

Restoration of compensation has been induced by oxygen therapy in some cases of intractable cardiac failure, including those with cor pulmonale and pulmonary emphysema, as well as in those with left ventricular insufficiency. Improved heart action and an increased excretion of chlorides (associated with CO_2 elevation in the blood and tissues) have been considered significant factors in the initiation of diuresis by oxygen therapy.[1-3] A diuretic response to administration of steroids has also been observed in some cases of heart failure that were refractory to routine measures.[4-8] Camara and Schemm[4] used corticotropin in the production of diuresis in patients with refractory heart failure, and Riemer[6] reported a similar result with prednisone in a patient with multiple myocardial infarctions and intractable cardiac decompensation. In our clinic, the use of prednisone was followed by prompt weight loss and increased urinary output in cases of pulmonary emphysema and fibrosis with cor pulmonale and in those without cardiac failure.[9]

The therapeutic activity of corticosteroids in the control of refractory cardiac failure may depend in part on a diuretic action that results from their ability to increase the glomerular filtration rate.[7] The steroid compounds may maintain the structural integrity of capillaries and hence prevent fluid loss from the intravascular spaces; the consequent increase in plasma volume may augment the glomerular filtration rate and thereby promote diuresis. The diuretic effect was found to be more marked in the delta-1 compounds, such as prednisone, than in the cortisone-hydrocortisone compounds that have an antagonistic sodium-retaining action. Riemer[7] suggested that steroids could exert their diuretic action by suppressing the output of other adrenocortical steroids, such as aldosterone, and thereby inhibit the sodium retention caused by the excess of aldosterone that may occur in heart failure. There is evidence that steroids also have inhibitory actions against pituitary antidiuretic hormone.[10]

A special effect of the use of steroids in cases of chronic pulmonary disease with cor pulmonale or left heart failure is the conspicuous relief of hypoxia resulting from improvement in alveolar ventilation. In such clinical entities as pulmonary emphysema and fibrosis and severe bronchial asthma, the administration of anti-inflammatory steroids presumably is followed by a reduction in edema of the bronchial mucous membrane as well as by relief of bronchospasm, increase in the patency of the airway, and a consequent rise in arterial oxygen tension.[11, 12] In cases of cor pulmonale, Dexter *et al.*[13] showed that, when hypoxia is absent, the cardiac output decreases in inverse relationship to the degree of pulmonary hypertension, and heart failure is rare; in the presence of hypoxia, the cardiac output rises. Cardiac failure depends on the association of hypoxia with a high degree of pulmonary resistance and occurs when the right ventricular myocardium is unable to raise the output, presumably because of poor oxygen supply. The administration of oxygen is a specific measure for the correction of these disturbances. The correction of hypoxia by the use of steroids in adequate dosage in suitable cases may provide indirectly a response similar to that obtained with oxygen therapy.

In our group of 50 patients with pulmonary emphysema and fibrosis treated with prednisone, a significant weight loss was noted in 12.[9] In 5 of these 12, the weight loss was largely the result of elimination of fluid accumulated during previous therapy with hydrocortisone. Of the remaining 7, 3 were in overt or borderline heart failure and 4 had pulmonary fibrosis without demonstrable heart failure. The cause of the diuresis and weight loss in these cases was not clear, but relief of hypoxia may well have had some causal effect similar to that noted by Barach and Richards[1-3] in the treatment with oxygen therapy of patients with chronic cardiopulmonary insufficiency.

The beneficial effects of prednisone in a severe case of chronic cor pulmonale secondary to pulmonary emphysema and fibrosis are strikingly illustrated in the following case report.

F.F., a 55-year-old stock broker, was admitted to the Presbyterian Hospital on October 18, 1958, for treatment of severe dyspnea and generalized edema. He had a history of almost continuous asthma since the age of 5 and had pneumonia as a child and in 1951; he had stopped smoking 15 years before admission. There was no family history of asthma or of extrinsic allergy. Extensive studies for tuberculosis were negative 27 and 8 years before admission, and a bronchogram made several years ago is said to have been negative.

In October, 1955, the patient began to develop typical signs of right and left ventricular failure with increased dyspnea, edema of the face, and pain in the region of the liver. The lungs sounded full of moist bubbling rales, rhonchi, and wheezes, and there was fluoroscopic evidence of pulmonary emphysema and pulmonary fibrosis, especially in the upper lobes; slight right ventricular enlargement was present. Prominent pulmonary artery pulsations were noted, and the electrocardiographic tracings showed right ventricular hypertrophy and strain; there was no polycythemia. At this time the patient responded well to digitalization, mercurial diuretics, and salt restriction, in addition to antiasthmatic therapy with aminophylline, ephedrine, and nebulized adrenaline.

In the summer of 1956 signs of heart failure reappeared during an exacerbation of asthmatic symptoms, and again were controlled on digitalis and mercurial diuretics. At this time pulmonary function studies were consistent with severe pulmonary emphysema; however, a decreased expiratory flow rate and reduction in vital capacity did not improve after bronchodilator aerosol. In June 1958 the patient again developed edema and cyanosis of the lower extremities. In spite of minimal asthma, dyspnea increased; the usual light-yellow mucoid expectoration decreased from 1 cup per day to a small amount. The patient developed marked weakness and anorexia. Fluoroscopic examination showed marked right ventricular enlargement in addition to the previously described changes. Hemoglobin was 14.1 gm. per cent, and the RBC count was 5,060,000.

The patient was continued on 0.25 mg. Digoxin 2 to 3 times a day. Chlorothiazide (500 mg. twice daily) was also given with supplementary potassium, without demonstrable effect on the edema. Parenteral Mercuhydrin and

Thiomerin failed to induce diuresis; partial relief of the edema followed the administration of mercuhydrin intravenously after 500 mg. aminophylline intravenously. The patient still failed to improve after 3 weeks of bed rest, and he became unable to walk more than 20 feet because of dyspnea. Nocturnal orthopnea increased, and the abdomen became swollen.

When the patient was seen on October 13, 1958, while awaiting hospitalization, he was started on 20 mg. prednisone daily. Within 5 days he noted considerable diminution of leg swelling, decrease of cold and clammy feeling in hands and feet, marked relief of dyspnea, diminution in wheezing, and recognizable increase in urinary output. His abdominal swelling did not change, and he was admitted to the hospital.

On examination, the blood pressure was 130/80 and the pulse was 119 per minute. The patient was moderately orthopneic; the peripheral veins were distended and there was generalized edema. His hands and feet were cold and cyanotic and moderate fingernail clubbing was present. The chest was barrel-shaped, percussion note was hyper-resonant, and diaphragms low and fixed in position. The lungs were full of inspiratory and expiratory rhonchi and moist rales were heard all over both lung fields. The cardiac apex was felt in the fifth intercostal space at the anterior axillary line. The rhythm was rapid and regular and a Grade-I apical systolic murmur was heard. The abdomen was distended; the liver was felt 3 fingerbreadths below the right costal margin. There was shifting dullness in both flanks.

Laboratory examination showed the following: hemoglobin, 12.7 gm. per cent; RBC, 4,600,000; and WBC, 7900 (with polymorphonuclears, 60 per cent; eosinophils, 2 per cent; lymphocytes, 33 per cent; and monocytes, 5 per cent). Hematocrit was 47.6; urine was negative for albumen, sugar, and microscopic matter; urea nitrogen was 30 mg. per cent; and sedimentation rate was 17 mm. after 1 hour. Cephalin flocculation and thymol turbidity were negative. Serum electrophoresis showed albumen, 3.6 gm. per cent with control, 4.2 gm. per cent. Globulins were normal; direct serum sodium, 138 mEq./l.; direct potassium, 6.7 mEq./l.; and venous pressure, 200 mm. saline. Protein-bound iodine was normal, and an electrocardiogram showed right-axis deviation and AV nodal tachycardia. Chest X ray showed considerable infiltration of undetermined etiology in the mid-portion of each lung, as well as in the left upper lobe medially. The lungs were emphysematous and the heart showed considerable over-all enlargement; the lateral view indicated right ventricular enlargement.

The patient's dosage of prednisone was increased to 40 mg. daily. Digitoxin (0.2 mg. daily) was given for 3 days, after which it was discontinued because of the nodal tachycardia. Nine days later, digitoxin was again administered, this time in doses of 1.2 mg. for the first 24 hours, and 0.1 mg. daily for maintenance. On the third and sixth hospital days, 2 cc. Mercuhydrin was given intramuscularly after an intravenous injection of 500 mg. aminophylline in 200 cc. of 5 per cent dextrose in water. A 5-gr. aminophylline tablet* was given on arising and a 4-gr. aminophylline tablet† at bedtime, as well as inhalation of nebulized 2 per cent neosynephrine hydrochloride with 0.4 per cent iso-

* Cardalin, Irwin, Neisler & Company, Decatur, Ill.

† Dainite "night" tablet, Irwin, Neisler & Company, Decatur, Ill.

proterenol* (0.5 cc. diluted with 1.5 cc. saline by mouth-rebreathing apparatus at 5 l. of oxygen per minute).

The patient experienced further relief of dyspnea 24 hours after starting treatment. He had a high urinary output; edema and signs of ascites and enlargement of the liver disappeared 1 week after admission to the hospital. His weight decreased progressively from 116 lb. on admission to 100 lb. after 10 days, as shown in FIGURE 1.

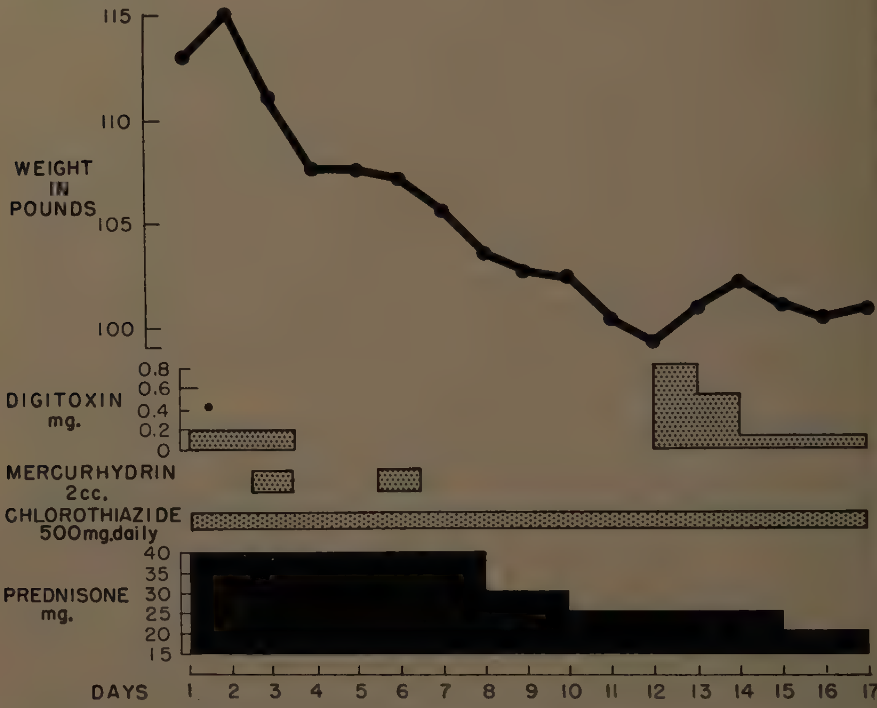

FIGURE 1. Diuresis induced by prednisone in patient with pulmonary emphysema and cor pulmonale.

Expiratory wheezes on physical examination decreased, and were gone by the end of the first week in the hospital. There was a marked increase of appetite, and the patient was able to take food amounting to 3000 calories. He experienced a marked increase in feeling of well-being and was able to sleep well on 1 pillow for the first time in 4 months. His hands and legs became warm, and cyanosis disappeared.

The dosage of prednisone was gradually decreased, beginning on the eighth hospital day, to a 20-mg. daily maintenance. The patient was discharged on November 3, 1958, after 17 days in the hospital; 2 days later he returned to work.

The response to oxygen inhalation (air and 40 per cent oxygen) during exercise is shown in TABLE 1. The pulmonary ventilation was determined after a standard Master 2-step exercise, with inhalation of compressed air as a control and, subsequently, while using a portable device supplying 40 per cent oxygen.* The control P.V. of 7.2 l./min. was increased to 15.3 after exercise with air and to 12.5 after exercise with 40 per cent oxygen.

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* Nebu-Prel, Thomas Mahon Co., Englewood, N. J.

Discussion

The determination of the minute volume of ventilation when the patient is breathing air compared to that when breathing 100 per cent oxygen has been used in our clinic since 1938 to provide an indication of the increased energy required in breathing because of overt or latent hypoxia. Since an oxygen exercise program was instituted 10 years ago, the decrease in ventilation during exercise (while inhaling 30 to 40 per cent oxygen) has been utilized to illustrate a physiological reflection of the value of this procedure, especially since portable apparatus for oxygen therapy has become more available for outdoor and home use. The use of steroid hormones, as well as exercise with oxygen, are factors that increase cardiorespiratory reserve.[14-16]

Among the factors that appear to be of crucial clinical importance in some cases, although not in the one cited above, is the rapidity with which a maximal degree of relief of bronchospasm is initiated. Since adrenal atrophy is present in a variable degree in patients treated with steroid hormones, the use of ACTH is frequently futile. In 2 cases (reported to the senior author) of pulmonary emphysema with severe bronchospastic dyspnea, in which there was lack of improvement after ACTH and relatively small dosage of prednisone, the fatal outcome was traced to unrelieved dyspnea. On the other hand, the prompt administration of 100 and 200 mg. of prednisone as an initial dose, repeated in 12 to 24 hours, has been found to be followed by a conspicuous relief of obstructive dyspnea. It may be assumed that constriction of the respiratory passageway is diminished as a consequence of the anti-inflammatory influence of the steroid hormone. The beneficial effect of high dosage of prednisone has been repeatedly observed in our clinic in the preoperative and postoperative care of patients with pulmonary emphysema in whom surgical extirpation of parts of the lung is carried out. When apparent lowering of the arterial CO_2 tension is accomplished by a pharmacological agent that initiates increased diffusion of CO_2 as well as oxygen, the patient is obviously improved, and in a way that is not accomplished by arbitrary mechanical hyperventilation. In the case history cited above, a state of intractable cardiac failure of 4 months' duration was relieved by administration of moderate dosages of steroids. In other patients very large dosages may be indicated.

TABLE 1

EFFECT OF OXYGEN INHALATION ON THE PULMONARY VENTILATION AFTER EXERCISE

	Liters per minute
Control before exercise	7.2
After Master 2-step exercise, breathing air	15.3
After Master 2-step exercise, breathing oxygen	12.5

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* Oxy-Hale, Controlled Pressure Inc., Erie, Pa.

Since it is clear that the increased efficiency of ventilation and the consequent relief of hypoxia initiated by steroid hormone therapy may result in physiological effects that are similar to those previously accomplished by oxygen inhalation, much of our knowledge obtained from studies in inhalational therapy may be applicable to the use of compounds such as prednisone. For example, it is known that an increase in the oxygen concentration of the arterial blood has in many cases relieved anginal pain and the symptoms of coronary insufficiency. The maintenance of improved diffusion of oxygen by pharmacological treatment that relieves bronchospasm may similarly decrease the likelihood of the symptoms of coronary insufficiency on exertion. In cases with chronic respiratory disease in the older age group, the incidence of overt or unrecognized coronary sclerosis may be assumed to be higher than in the general population; therefore, measures that maintain a normal or nearly normal arterial tension, at rest and on exertion, would tend to be beneficial in this respect.

It is appropriate to mention the impressions we have gained of the value and also the hazards of the administration of steroids, since our first report.[11] It is evident that the treatment of respiratory disease, including bronchial asthma and the bronchospastic type of pulmonary emphysema, has been revolutionized by the therapeutic results obtained with steroids, while, at the same time, complications have been reduced as the drug was improved and the skill of the physician in its employment increased. The complications of steroid therapy have been less severe and less common than originally encountered and expected. The incidence of peptic ulcer is very small in the group in which routine antacid treatment (aluminum hydroxide or calcium carbonate 1 to 2 hours after eating and on retiring) was given. Reactivation of pyogenic infection has taken place more frequently, but I know of no instance in our series in which this complication was not ultimately managed.

During the use of cortisone and ACTH, there have been instances of cardiac failure due to the sodium-retaining quality of these drugs. With their abandonment and with the employment of prednisone, no such complication has been found. The changes in the body have, however, been present in a large number; the weight gain, the increase in the girth of the abdomen and trunk, and the so-called "moon face" have been difficult to handle. The development of diabetes in some cases has not been a major complicating illness, since there are measures by which this illness can be treated.

In the evaluation of a new agent such as dexamethasone, the effect on the patient of the novelty of the drug should be kept in mind. This is particularly true in patients with asthmatic or allergic conditions in which a state of refractoriness develops to the medication given, including not only epinephrine and its derivatives, but also compounds, such as theophylline, of a quite different class. When patients with bronchial asthma or the bronchospastic type of pulmonary emphysema are treated with a new agent, a much more effective response may take place than when the patient has been on this drug for a considerable period. A precise evaluation of dexamethasone at this time is difficult. Various reports rate its therapeutic action as five to twelve times greater than that of prednisone. If one were to use isoproterenol instead of epinephrine as an aerosol in asthmatic patients who had become refractory to epinephrine, one could say that the former drug was many times more powerful than the latter, or vice versa, if the situations were reversed. To what extent this is true of steroid compounds cannot be answered precisely, but that this principle plays a role has been made clear to us a number of times. In our experience, dexamethasone appeared to be five to six times more powerful than prednisone. We do not know that it has fewer side effects than prednisone or whether it possesses in as high degree the capacity to produce feelings of well-being.

Summary

A case history of a patient with pulmonary emphysema and cor pulmonale is presented in which the administration of steroid hormone was responsible for the termination of intractable severe cardiac failure of four months' duration. The specific diuretic effect of the steroid hormones in cardiac failure associated with chronic pulmonary disease appears to be based in part on physiological alterations similar to those achieved by oxygen inhalation and in part on complex influences not yet clearly understood.

The factors involved in the relief of hypoxia by these agents include reduction of bronchial constriction by elimination of bronchospasm and diminution of edema of the bronchial mucous membrane, and improvement in the diffusion of oxygen and carbon dioxide.

An appraisal is given of the use of steroid hormones during the last decade in the treatment of severe bronchial asthma, bronchospastic type of pulmonary emphysema, and associated clinical entities.

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Discussion of the Paper

Question: Does Barach advocate the abandonment of the bronchodilator aerosols?

Russell L. Cecil (*Cornell University Medical College, New York, N. Y.*): I ask Barach if the physician should continue the use of prednisone indefinitely as a preventive of relapse, after the acute symptoms have subsided and the patient is brought under control and made comfortable. That question, of course, comes up in the treatment of rheumatic disease. It has always seemed that these steroids play their most wonderful and useful part in acute situations, and I wonder if, in the case of chronic respiratory disease, it is necessary to continue the prednisone after the acute symptoms have stopped.

Question: Do you advocate the early use of steroids in diseases that you know will lead to pulmonary fibrosis?

Alvan L. Barach: I do not advocate the abandonment of bronchodilator aerosols. Among the symptomatic methods of treatment of bronchial asthma and the bronchospastic type of pulmonary emphysema, the inhalation of bronchodilator aerosols is one of the most valuable and least harmful. Our position in respect to the use of corticosteroids is to add the amount of steroid hormone that is required above and beyond the maximum amount of physiological therapy, antibiotic therapy, or any other therapy that may be effective in these conditions. We make a sharp distinction between the treatment of bronchial asthma and that of pulmonary emphysema. In bronchial asthma the parenchyma of the lung is generally good, and our aim in these cases is to discontinue steroid therapy following the acute episode; with a good remission it sometimes happens that the individual will remain controlled for months by the inhalation of bronchodilators, oral bronchodilator medication, the use of iodides, and the variety of other measures employed to treat asthma.

I do not advocate the use of steroids to prevent, but to treat cor pulmonale in pulmonary emphysema.

There is only a limited number of patients with bronchial asthma who actually develop pulmonary emphysema in association with viral or pyogenic infection; this is about 15 per cent in our series of long-standing severe asthma. However, in the older patients who have pulmonary emphysema the problem is more complicated. Our approach is to determine how much improvement can be obtained by the development of diaphragmatic breathing and the use of bronchodilator aerosols. If the available therapeutic procedures provide inadequate relief, the addition of steroids may afford crucial benefit in the presence of demonstrable bronchospasm (about 40 per cent of cases). The degree of improvement in patients who have only muscular hypertonia of the bronchioles is not adequate to justify the use of a steroid except when there is, in addition, acute infection or acute inflammatory congestion. In those instances the use of the steroid with antibiotics may be, of course, lifesaving.

I make the point that, in cases of severe bronchospastic pulmonary emphysema with cor pulmonale, an initial dose of 100 mg. of prednisone by mouth is indicated. If it is given intramuscularly, a larger amount may be required. If small doses are employed, the patient may obtain little or no relief from severe dyspnea, and the outcome may be fatal.

MANAGEMENT OF CHILDHOOD ALLERGIES WITH ANTI-INFLAMMATORY STEROIDS

Samuel C. Bukantz

Jewish National Home for Asthmatic Children and the Children's Asthma Research Institute and Hospital, Denver, Colo.

The past decade of experience with the anti-inflammatory steroids has merely laid the basis for future studies. The observations reported here are only a beginning, insofar as I am concerned, and were made during a period of private practice that terminated in July 1958 when I assumed my present position at the Jewish National Home for Asthmatic Children. Here a somewhat different opportunity presents itself, the approach to which I hope to make evident during this presentation.

During the course of these observations I have found it useful to add to the standard definition of allergy a phrase that may be somewhat controversial: "The allergic symptom is one that can be reversed by anti-inflammatory steroids." This added sentence includes the asthmatic paroxysm. I share with my colleagues the feeling that this is not a complete definition, but I believe it is functionally correct, useful and true for the bulk of the situations, both acute and chronic, with which I am concerned at present.

Before continuing this presentation I propose to comment on some of the terms used and some of the experiences presented elsewhere in this monograph. First, what is the clinical meaning to us of the word potency? This is a term to which pharmacologists, organic chemists, and many of our clinicians refer constantly, and I fear that we tend to confuse clinical potency with weight potency. I suggest that we think about potency in terms of "Does it do something more insofar as tissue and disease are concerned?" or "Are we accomplishing the same biological effect with a smaller amount of something?" At present it is my conclusion that, among the many anti-inflammatory steroids available for clinical use, potency still remains the same biologically, with some changes in the milligram dosage and in the frequency and severity of some of their nontherapeutic effects.

Second, Sibylle Tolksdorf has intimated that the problem of infection is a greatly overrated one and that, from time to time, other investigators have made the same assertion. Conrad Riley has even hinted that we may be a bit superstitious about the use of antibiotics, and I agree with all of this. On the other hand, when infection is present and is aggravated by the concomitant use of the anti-inflammatory steroids, this may become a very important matter, and what we must do is clearly to define the circumstances in which infection requires special care and how, under such conditions, the decision regarding use of antibiotics is made and how the particular antibiotic is selected.

Third, Philip Hench asked Bram Rose about the incidence of arthralgias in the withdrawal phase of the therapy of allergic diseases in the adult. I was particularly interested in that question and in Rose's answer, because I have been constantly on the alert about panmesenchymitis as described originally by Slocumb's group as a withdrawal phenomenon.[1, 2] The investigators at the Mayo Clinic, Rochester, Minn., believed the condition occurred only in the withdrawal phase of the therapy with anti-inflammatory steroids of the rheumatoid diseases. I have encountered this condition with somewhat greater frequency than Rose has intimated: perhaps twice his frequency, which, as I recall, was 1 or 1½ per cent. I have seen the characteristic syndrome in the withdrawal phase of the therapy of allergic disease in the child, with all the phenomena described by Slocumb for the rheumatoid adult.[3] In either the adult or the child these may be instances of arthralgias or myalgias of such severity as to induce disability. I recall very well one instance in a pianist in whom arthralgias of the interphalangeal joints were so severe as to interfere with his art, and one 9-year-old professional dancer who had similar difficulties with his knee and hip joints. In none of the cases I have seen has there been evidence of previous joint symptomatology.

There are special biological problems in the child, since the child is a growing animal with a lower adrenocorticoid output capacity in his earlier years. This is revealed by some ingenious studies made with extracts of excised pituitaries from young or newborn healthy children.[4] Assays with such extracts have established the fact that the lower adrenocortical capacities of childhood are not related to lower pituitary corticotropin secretion, but are the result of intrinsically functional impairments or functional immaturities of the adrenal cortex. We have therefore the added problems presented by a growing animal whose initially reduced capacities for adrenocortical output are being subjected to treatment with extraordinarily powerful agents having great influence on the growth capacities of the child and the usual effects on adrenocortical function. Nevertheless, I think it is perfectly possible at all times in both the child and the adult to use therapeutic doses in both short-term and long-term courses (especially the former) without encountering the complications that are usually called side effects and that result from the varied metabolic activities of these agents. The primary clinical requirement to accomplish this is the closest possible supervision of the subject under therapy. Frequently the treatment goes along so innocently and so well that there is a tendency to relax a little or to become careless, and I think that this is wrong and dangerous. The maintenance, at all times, of a very close contact with patients under therapy with anti-inflammatory steroids is perhaps the most important factor in the avoidance of significant "complications."

A second and almost equally important requirement is a thorough knowledge of every metabolic action of the anti-inflammatory steroids; only by an intimate understanding of the mechanism of these activities will it be possible to achieve therapeutic effects with a minimum of side effects.

A note of tribute is also in order to the chemists whose continued efforts are to dissociate those properties that induce side effects from those that cause the desired therapeutic effects. The ingenious presentations of the chemists in this monograph suggest that some day this problem may be solved. Let us hope so!

A brief review of the complications of sterotherapy can be facilitated by using illustrations from an earlier article.[3] It is very difficult, with our present preparations, to control allergic states by using dosages of steroids that are not productive of any of the side effects. This is especially true of such intractable asthmatic children as I now see in Denver. It is more difficult to obtain incomplete but clinically significant therapeutic control of intractable asthma without having some degree of moon facies. It appears to make no difference which of the metisteroids we use or whether we use dexamethasone, although my experience with the latter drug is too limited to have much meaning. Moon facies, reflecting hormonal excess, requires especial concern and avoidance in childhood, since it may presage other more serious effects of overdosage. In preventing this condition, I do not know whether there is any advantage in calculating dose per square meter of body surface, as the Boston group does,[5] or whether one should utilize, as Forsham does, the daily urinary excretion of steroids.[6] I think that calculations by either method will give satisfactory results. We have calculated dosage according to square meters of body surface and have tried to maintain, with metisteroids, less than 7 mg./sq. m. body surface to remain within the nongrowth-arresting range. In any event, even if one does temporarily reduce growth, there is a prompt resumption when the drug is discontinued.[5]

Comment is made elsewhere in these pages about osteoporosis and the newer drugs in relationship to calcium excretion. There is at present some difference of opinion among our investigators as to whether dexamethasone does or does not promote an increased excretion of calcium. In any event, there are some things that we can do to combat osteoporosis, and new hormones may shortly be available, a growth hormone perhaps, as well as other anabolic hormones, that may help in the control of such phenomena. All of the hormone-excess phenomena are reversible and controllable; they can be tolerated for a short period of time, and they do not materially interfere with the clinical course.

The problem of psychosis and corticosteroids is one that I shall pass over at this point since I am uncertain as to the mechanism. I am not sure, for example, that it is wise to withhold the drugs from prepsychotic patients. There is good evidence to show that there may actually be amelioration of some allegedly psychotic symptoms while the corticosteroids are given, and I have an extraordinarily interesting example of this in a prepubescent male child under clinical study at the present time. I am not certain, either, when psychosis apparently develops during therapy, that this is a *de novo* phenomenon. When such an event supervenes, however, discontinuance of steroids would seem to be proper. It seems to me these are reversible diseases as well, and there is much more to be done in this area, initial steps toward which are in progress at our institution at the present time.[7]

The problems of tuberculosis and histoplasmosis have received much attention in this monograph, so I shall not consider here the precautions needed. As to viral infection, differences of opinion range from the warning that one must be very careful about such diseases as chicken pox in children, lest the infection become fatal under steroid therapy, to suggestions by other investigators that the corticosteroids be used for the treatment of such terrible and frequently fatal complications of varicella as the pneumonia that occurs more often in the adult.

I have intimated that with bacterial infection one must use the utmost caution. There is certainly evidence that one can increase microbial virulence and decrease host resistance to bacterial invasions. An early recognition of the presence of infection by studying stained smears of nasal and bronchial secretions is extremely helpful in preventing some infectious complications during sterotherapy. Bacteriological cultures are indispensible for optimal management of bacterial complications, and the indications for antibiotic therapy are no different than in nonsteroid-treated cases; it is only that caution must be even greater. I know that I have discussed this matter very often with my colleagues in pediatrics and with those who have had experience in treating chronic pulmonary and upper respiratory disorders. Differences of opinion among the experts still are typical. With the special problem confronting us we must be especially careful lest we create resistant strains of bacteria, thus denying to ourselves the availability of an important antibiotic when really urgent need for its use arises. This consideration poses a particularly difficult problem and one that deserves the most intensive study and deliberation.

As for gastrointestinal ulcers: I am delighted by Palmer's presentation. Perhaps worry about this complication is unnecessary. It certainly is not a major problem in pediatrics in my experience.

It is apparent that a distinction must be made in anti-inflammatory steroid treatment of seasonal and perennial allergic problems. Among a series of ambulant children and adults observed for several years, the duration of therapy was much shorter in the seasonal cases, as would be expected, and seldom exceeded a course of one month, in contrast to perennial cases.[3] Among the 39 allergic children in this series I call attention particularly to the coadjuvant use of antibiotics in their management at the time that this study was made. We felt it necessary to give antibiotics far more often to perennial sufferers than to the seasonal ones. Again, this is to be expected, since perennial disease is much more likely to be associated with a bacterial infection.

As to the duration of therapy, we have encountered much more difficulty in discontinuing the steroids with the perennially symptomatic patients. Quite a few of these were still on the steroids after 2 to 5 months and even after 6 months. My aim and objective at present is to treat for as short a period of time as is essential and to withdraw as quickly as possible, working on the assumption that complications have a direct relationship (both as to incidence and severity) to the duration of treatment. This is certainly not crystal clear, however, in the light of the problem of biological cure that I think Riley is aiming at to some extent with his nephrotics. I have heard Sulzberger describe one of his cases of pemphigus that was apparently cured after many years of treatment with anti-inflammatory steroids.[8] The fact that biological cure may occur after a long period of suppressive treatment with the anti-inflammatory steroids gives one courage and hope. Perhaps a study should be initiated in other diseases, the design of which would include deliberate protraction of therapy with the anti-inflammatory steroids for very long periods during apparent quiescence of disease. This would be quite different from our present tendency to withdraw and discontinue the steroids as soon as possible after symptoms are controlled.

One of the most distressing conditions in the asthmatic population, both in childhood and in the adult, is the intrabronchial accumulation of variable amounts of a homogeneous acellular thick mucus. When sufficient in quantity, this matter contributes to the death of asthmatics by internal obstruction.[9, 10] One of our research objectives is to try to understand something of what the anti-inflammatory steroids may do to the whole mysterious process by which this mucus accumulates. Whether this is present in large or small degree, and I think it is present in many, if not all, of the perennially asthmatic patients, it is possible that some of the beneficial effects of anti-inflammatory steroids in the management of asthma result from a combination of actions among which is the reversal of the production of mucus or a reduction of its viscosity.

Table 1 represents our recent experience at the Jewish National Home for Asthmatic Children (JNHAC). Admissions to the home for the year ending June 30, 1958, consisted of 88 patients, of whom 75 per cent had been on some dosage of anti-inflammatory steroids prior to admission and of whom 44 or 50 per cent were still taking these drugs at the time of admission. Contrasting the experience since July 1, 1958, would indicate that we are getting an even higher percentage, as much as 97 per cent of our patients, who were on these drugs prior to admission. This observation is only by way of indicating that, with increasing emphasis on the criteria of intractability in our selection process, we shall continue to find, I think, that virtually all admitted patients will have had at least one trial of anti-inflammatory steroids. It has become almost a criterion of severe intractability that the child who is resistant to the usual forms of therapy in his own community will have received anti-inflammatory steroids and is probably still on these drugs upon admission.

TABLE 1

HISTORY OF ANTI-INFLAMMATORY STEROID (AIS) THERAPY AMONG NEW ADMISSIONS AT JNHAC

Category	July 1, 1957 to June 3, 1958		July 1, 1958 to November 30, 1958	
	Number	Per cent	Number	Per cent
Total admissions	88	—	32	—
Previous AIS therapy	65	75	31	97
Maintenance AIS on admission	44	50	19*	59
No previous AIS therapy	23	25	1	3

* Three additional cases were on AIS until 5 to 21 days preceding admission.

Table 2 indicates what our experience is with discontinuation of the drugs after the child comes to JNHAC. This table illustrates the frequency of discontinuation in 2-month periods from 1 year to 1 or 2 months following admission. It is of interest that, of the 44 patients on steroids at the time of admission, administration could be discontinued in 11 or 25 per cent after 1 month of residence and in 11 other patients, or an additional 25 per cent, after a second month, making 50 per cent in 2 months. After that, we could discontinue treatment of 3 after 3 months, and beyond this we found ourselves contending with a population of patients in whom we could not discontinue the anti-inflammatory steroids. Thus, a fairly appreciable fraction of our patients, representing a most important biological group of intractable asthmatic children, cannot tolerate withdrawal of corticosteroids despite close and careful medical supervision.

Table 3 indicates the parallel experience in the shorter 5-month period since

July 1, 1958. Of the 19 patients who were on anti-inflammatory steroids at admission, we are still continuing 11 on AIS although, of course, some of them have been with us for a period of only 2 months. The 8 patients in whom treatment was discontinued, however, represent less than the 50 per cent we were able to discontinue in the first group. It is close to that, however.

FIGURE 1 illustrates an experience with AIS therapy of atopic dermatitis and asthma combined. The relative clinical severity of each condition has been estimated and graphically represented. It will be noted that there was no asthma during a period of treatment for a severe eczema. After the eczema came under control and the steroids were progressively reduced, there was a recurrence of asthma, and this was without relationship to any seasonal factors. The dissociation of the two therapeutic effects suggests the possibility that there may be some biologically significant fact in this observation that deserves investigation.

TABLE 2

RATE OF DISCONTINUANCE OF AIS AFTER ADMISSION TO JHNAC
(July 1, 1957, to June 30, 1958)

Length of residence (months)	Number of children admitted	AIS discontinued (months)												Still on AIS
		1	2	3	4	5	6	7	8	9	10	11	12	
12 to 11	14	2	4	1	1	0	0	1	0	0	0	1	0	4
10 to 9	5	1	1	0	0	1	0	0	0	0	0	—		2
8 to 7	7	1	2	1	0	0	0	0	0	—				3
6 to 5	6	3	2	0	0	0	0	—						1
4 to 3	4	0	1	1	0	—								2
2 to 1	8	4	1	—										3
Totals	44	11	11	3	1	1	0	1	0	0	0	1	0	15

TABLE 3

RATE OF DISCONTINUANCE OF AIS AFTER ADMISSION TO JNHAC
(July 1, 1958, to November 30, 1958)

Length of residence (months)	Number of children admitted	AIS discontinued (months)					Still on AIS
		1	2	3	4	5	
5	6	0	3	0	0	0	3
4	3	0	1	0	0	—	2
3	2	0	0	0	—	—	2
2	3	2	1	—	—	—	0
1	5	1	—	—	—	—	4
Totals	19	3	5	0	0	0	11

FIGURE 2 is of another patient, with the combination again revealing that a course of management of asthma and eczema may evidence a dissociation of the severity of the two illnesses in a given patient, and that in the same patient the two conditions respond somewhat differently to control with the steroid drug.

FIGURE 3 represents observations made on the only patient in our series in whom diabetes had been induced. This is a child with rheumatic fever, not suffering with asthma at the moment, although she was known to have had this condition. She was treated in accordance with the recommendation of our pediatric cardiologist, who recommended the use of 60 mg. of prednisolone

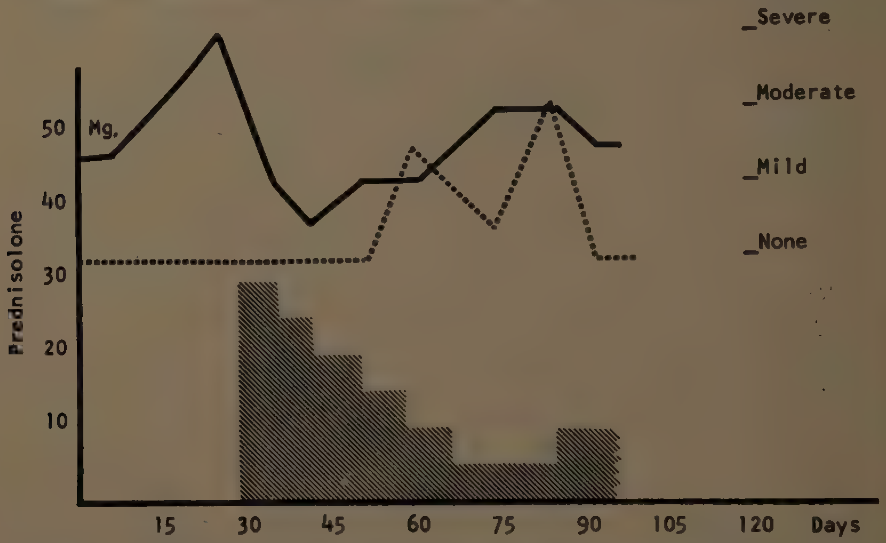

FIGURE 1. AIS therapy of combined atopic dermatitis and asthma (patient J.B., aged 11 years). *Solid line*, eczema; *broken line*, asthma and rhinitis.

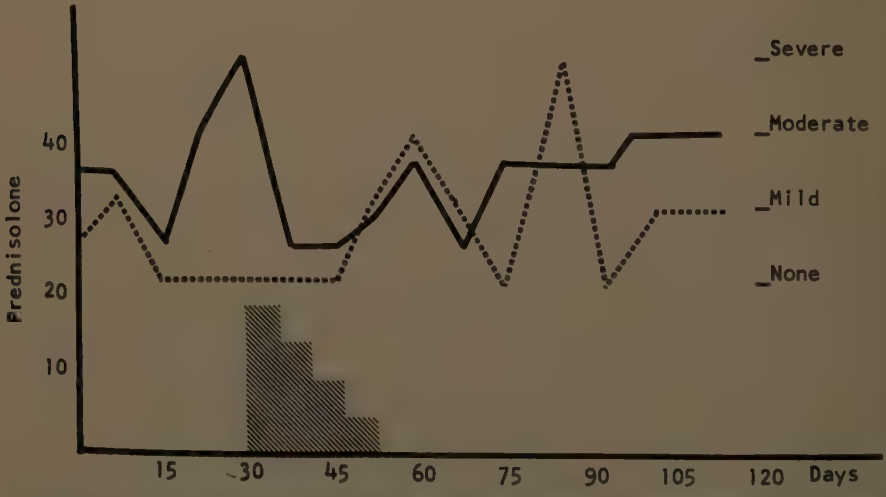

FIGURE 2. AIS therapy of combined atopic dermatitis and asthma (patient R.W., aged 8 years). *Solid line*, eczema; *broken line*, asthma.

daily for 30 days, after which the child developed diabetes, having gone through practically all of the important side effects, from euphoria and moon face to acne, abdominal pain, and then a yeast infection of the perineum. Finally, we shifted to dexamethasone, which did not materially affect the course of the diabetes, and a progressive weight gain seemed even more accelerated following the dexamethasone.

FIGURE 4 illustrates several glucose-tolerance curves on the same patient. These curves show that doses of dexamethasone comparable to prednisolone

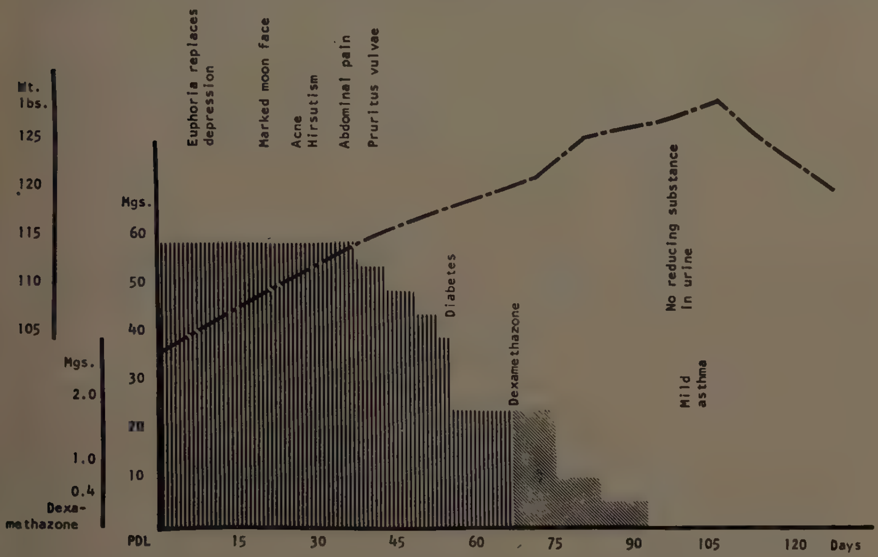

FIGURE 3. Weight response (*interrupted line*) in patient A.S., aged 11 years. Diagnosis: rheumatic pericarditis and bronchial asthma.

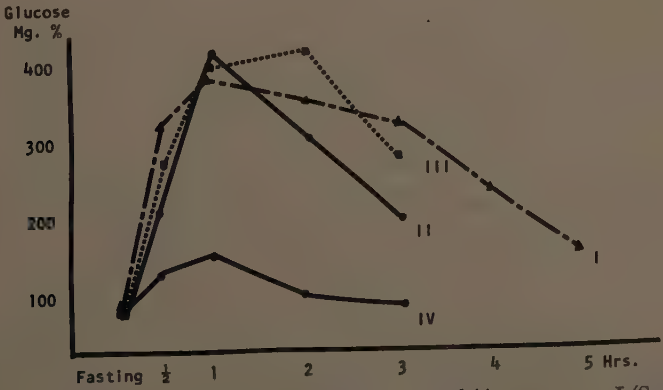

FIGURE 4. Glucose tolerance curves of patient A.S., aged 11 years: curve I (September 24, 1958), on prednisolone (40 mg./day); curve II (October 7, 1958), on prednisolone (25 mg./day); curve III (October 14, 1958), on dexamethasone (2 mg./day for 6 days); and curve IV (November 11, 1958), 8 days after the discontinuance of anti-inflammatory steroids.

had no effect upon the diabetes that had been induced by prednisolone. The diabetes was not ameliorated during the course of a 6-day period of treatment with dexamethasone, but curve IV reveals prompt return to normal levels 8 days after discontinuance of all steroid drugs. It should be noted that fasting blood sugars were regularly normal throughout the period of diabetes.

In conclusion, I would say only that we have more to learn than we know, but that we can nevertheless employ anti-inflammatory steroids with considerable safety in managing childhood allergies. This is particularly true for asthma and, if appropriate precautions are taken, we can limit complications to a negligible incidence. These drugs may very well be lifesaving measures, although we may, in the course of our use of them, create new and interesting biological problems. From among children who suffer from allergies and, especially, from intractable asthma, the anti-inflammatory steroids may be permitting the selection of a population of patients of special biological characteristic and of quite extraordinary interest for future study.

Acknowledgment

I take this opportunity to express my appreciation to Schering Corporation, Bloomfield, N. J., for their generous supplies of drugs, without which these observations could not have been made.

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Discussion of the Paper

QUESTION: I was very much interested in the table Bukantz showed of 19 children with protracted asthma. As you recall, he mentioned that they were at the Jewish National Home for Asthmatic Children for 5 months and, in this period, less than 50 per cent were taken off corticosteroids. Am I right in assuming that these patients did not respond during that long period of 5 months? It has been my impression that, at the home to which these patients were admitted, response is usually more rapid because of environmental change, change from home life, and such psychosomatic reasons. From what Bukantz showed, it is evident that as long as 5 months was required, with or without corticosteroids, and still at least 50 per cent of the asthmatic children were uncontrolled. Maybe this small group is unusual, but possibly Bukantz can explain why more clinical improvement did not result in these asthmatic children after such a long period of environmental change.

WALTER L. PALMER (*University of Chicago School of Medicine, Chicago, Ill.*): Perhaps a comment is in order on the nervous complications of steroid administration. Without attempting to give any statistical data (because we have none), I must say that we are convinced that in certain patients emotional disorders, in addition to straightforward psychoses, are extremely important. Of 240 steroid-treated patients with ulcerative colitis, already mentioned, 3 committed suicide. They may have done so for many reasons, but in at least 2 there was rather clear evidence that the steroid precipitated a psychotic state.

We try to be careful of these emotional factors. Of course, ulcerative colitis is a disease in which emotional factors are extremely important, as is the case also in bronchial asthma and in a great many other conditions in medicine. Psychotherapy, as we all know, is extremely valuable and should be employed in conjunction with other therapy. However, the reason I mention this subject is that Kirsner and I are convinced, purely on the basis of clinical observation, that the use of sedatives and the modern tranquilizing drugs from meprobamate to such agents as chlorpromazine and promazine can be extremely helpful in the control of these symptoms.

ALVAN L. BARACH (*College of Physicians and Surgeons, Columbia University, New York, N. Y.*): May I comment on Palmer's last remark? I have a short film that illustrates the influence of psychosomatic factors in one patient in whom a very severe state of status asthmaticus was provoked directly by an emotional disorder that led to hyperventilation. Hyperventilation is the one method by which we can illustrate, demonstrate, and prove without question the importance of emotional factors. A man who breathes at twice the normal pulmonary ventilation rate creates an effect almost comparable to reducing the bronchial diameter by half. Furthermore, by reason of overblowing of CO_2, he may develop laryngospasm, bronchospasm, and tissue hypoxia of such nature that death itself may be produced by the emotional disorder that causes hyperventilation.

I do not know that I have ever seen bronchospasm take place directly without an initial hyperventilation episode, the mechanism of which, of course, can be clearly seen if one watches the movement of the upper chest both in children and in adults. I endorse what Palmer has just said and add that it is through a hyperventilation physiological sequence that both laryngospasm and bronchospasm take place.

I wonder if Bukantz sees in asthmatic children the complications that we see in adults following the administration of antihistamines. In about one of four of our cases of intractable asthma the intractability is due to excessive use of antihistaminic drugs that dry the mucus along the tracheobronchial tree to such an extent that prolonged asthmatic dyspnea and cough may take place.

Recently, we observed a woman who, despite large doses of steroids, remained in status asthmaticus for 11 weeks. It was my belief that the drying effect of antihistaminic drugs was pronounced. I urge that, in any case in which the response to steroid therapy is slow, one should determine how much antihistamine has been given.

SAMUEL C. BUKANTZ: As to the relatively large number of children who required prolonged steroid therapy: I think this may be due to the fact that with the kind of selection we are now attempting we are admitting many more severe cases. I am inclined to say that it is not simply a change of environment or even careful long-term medical care that can produce a magical solution for all wheezing children, and I am sure that this is equally true of the wheezing adult.

Since I am at an institution that has always exhibited an intense interest in the psychological aspect of asthma, it was very refreshing to have it pointed out that we are not paying enough attention to it. I hope that this does not give the impression that we are not. As a matter of fact, the second most extensive service that we have at the home is a psychological service in which I think we are making very strong efforts to comprehend the nature of the problem and to treat the emotional aspects as indicated.

I do believe that some of the observations on the nervous manifestations evoked by corticosteroids in your adult patients reflect not adult-child differences, but dosage differences. We constantly try to use minimal maintenance dosage therapy, while you, unfortunately, must use large-dose therapy, and the effects on the central nervous system of these two extremes are quite different.

Finally, concerning tranquilizers, I share completely your feelings about them. What we should like to do is to establish a control study with the aid of the psychopharmacological service center of the United States Public Health Service in Bethesda, Md.

With reference to Barach's question, I think that it is perfectly possible that some of the children were subjected, prior to their admission, to long-term antihistaminic therapy, and that this may play a part in the thickening of secretions. My own feeling about the secretions is that they have some other pathogenic mechanism for their accumulation and, as you know, I am trying to determine what that mechanism is. I do not think that prolonged antihistaminic administration is at all the complete answer to why they accumulate, although it may play a part. At the Home we do not give antihistamines to our asthmatic children, so that this is not something to which we contribute.

THE CORTICOSTEROIDS IN THE MANAGEMENT OF DISEASES OF THE SKIN*

Victor H. Witten

Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, and the Skin and Cancer Unit of the New York University Hospital, New York, N. Y.

From the outset, the skin and visible mucous membranes have lent themselves well to the study of the therapeutic effectiveness of the corticosteroids, whether administered topically or systemically. It was only natural that an organ such as the skin, which is always exposed and readily available for examination, should be used for systematic therapeutic assays of each of these compounds as they were introduced. As a result of such investigations it soon became apparent that the corticosteroids could benefit many dermatoses that previously either plagued the sufferer or resulted in death simply because an effective means of therapy was not available. It was soon evident, however, that, in the high doses often required, the undesirable effects produced by the systemic administration of these compounds were of such a nature and degree as to limit their therapeutic applications. On the other hand, the external corticosteroid preparations have proved to be perhaps the greatest single advance in topical dermatological therapy and, with but one exception, may be used freely and without harm.

The Systemic Use of Corticosteroids

In 1950 Marion B. Sulzberger and I, in private practice, began prescribing the first of these compounds (cortisone acetate) to become available by mixing a solution with raspberry syrup for oral administration in the management of selected diseases of the skin. It was evident from the very beginning, however, that this agent was not curative, but acted to arrest the disease or even clear it completely if an adequate dose was given and maintained. Sulzberger has referred to this effect of suppressing the disease manifestations as "morbidistatic."[1]

Since those early days it has been proved that this morbidistatic effect can be used to distinct advantage in the successful management of many diseases of the skin. This is true whether the corticosteroid is administered for short or long periods.

For short-term use corticosteroids are very helpful in managing such severe self-limited acute dermatoses as (1) eczematous contact-type dermatitis; (2) acute urticaria and angioneurotic edema; (3) certain drug eruptions (for example, urticarial, purpuric, and bullous); and (4) erythema multiforme.

In the management of these diseases the effective morbidistatic dose ordinarily need not be maintained for longer than a few days or perhaps a few weeks. Used in this manner, the corticosteroids relieve the untold suffering caused by these often very pruritic and completely incapacitating eruptions, which may be localized or widespread. Furthermore, according to our own observations

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there is no evidence that the short-term administration of corticosteroids in any way interferes with the natural course of the disease; thus, it neither prolongs nor shortens it. It has been our impression at times, however, that some individual cases of acute, self-limited dermatitis have run a shorter course than anticipated, had the patient not received corticosteroids.

During the short-term administration of corticosteroids, the complications that sometimes occur ordinarily are minor, and it is not usually necessary to discontinue the drug because of them.

The prolonged systemic administration of corticosteroids (that is, for longer than 2 months)[2] plays a most important role in the management of selected severe and refractory cases of ordinarily nonfatal, chronic, or recurrent dermatoses such as (1) atopic dermatitis (including infantile eczema); (2) exfoliative erythrodermas; (3) nummular eczema; (4) eczematous or pustular eruptions of the hands; (5) distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe); (6) chronic urticaria; (7) seborrheic dermatitis (particularly when widespread and in intertriginous areas); (8) incapacitating widespread or exanthematous psoriasis (when proved refractory to other measures, including selected forms of radiation therapy); (9) widespread acute exanthematic lichen planus; and (10) severe alopecia areata and generalisata, which is unbearably disturbing and at times incapacitating.

TABLE 1

AVERAGE SCHEDULE OF CORTISONE REDUCTION*

Cortisone received daily mg.	Permissible amount of each reduction mg.
500 or more	50
100 to 500	25 to 50
25 to 100	12.5
0 to 25	2.5 to 5

* Data from Sulzberger *et al.*[3]

Once long-term therapy has been undertaken for any of these dermatoses and after the disease has been brought under control by sufficiently large doses of the corticosteroid, the daily amount should be very gradually reduced, depending on the response of the patient. The reduction of dose is carried out stepwise, following in principle the schedule shown in TABLE 1.

Every effort is made to avoid giving more of these hormones than is absolutely necessary. This means that the disease and its symptoms should be kept under reasonable control, but not completely subdued, for it is only by the presence of some dermatitis or some slight complaints from the patient that the physician may know that he is not giving more corticosteroid than is actually required.

On long-term therapy it is extremely important that the patient be examined regularly in order to evaluate the effectiveness of the drug, to look for possible undesirable effects, and to adjust the dosage as necessary. The complications for which one must be on the alert are listed in TABLE 2.

From time to time we hear it stated that corticosteroids should not be prescribed for nonfatal and nonserious diseases. While none of the diseases listed above is fatal, all may be serious in that they are sometimes totally incapacitating. As Stephen Rothman so well stated, there are "diseases which do not endanger life, but ruin it." Prior to the use of corticosteroids there were innumerable persons with skin diseases that had actually ruined their lives; today, with these new potent compounds, these persons need suffer no longer.

TABLE 2

COMPLICATIONS OF SYSTEMIC CORTICOSTEROID THERAPY*

MAJOR

Adrenal insufficiency
Compression and other pathological fractures
Disturbed metabolite balance (sodium and potassium)
Hypertension (when marked)
Muscle wasting
Osteoporosis (for example, vertebral, hip)
Peptic ulcer
Psychoses (for example, manic, depressive)
Systemic intercurrent infection (for example, tuberculosis, septicemia, disseminated chicken pox)
Thromboses
Uncontrolled diabetes
Uremia

MINOR

Abdominal fullness or bloating
Acneiform lesions
Decreased appetite
Gastric distress
Hirsutism
Hypothyroidism
Increased appetite
Mild glycosuria or hypertension or both
Mild psychic changes (for example, irritability, euphoria, restlessness, insomnia)
Pedal edema
Petechial and purpuric skin lesions
Regional "fat" distribution (for example, facial mooning, buffalo hump, supraclavicular fat pads)
Tremors and paresthesias
Weight gain
Weight loss

* From Sulzberger *et al.*[3]

There remain a few ordinarily fatal dermatoses that are not only aided by the corticosteroids, but are sufficiently controlled so that the patient may actually be kept alive and, in most instances, capable of meeting the responsibilities of life; these are (1) pemphigus (all forms), (2) acute and subacute systemic lupus erythematosus, and (3) acute phases of dermatomyositis.

While the systemically administered corticosteroids are not credited with the cure of disease, I repeat that many patients with potentially fatal diseases such as those mentioned are alive today after systemic treatment with corticosteroids. While it is possible that a very small minority of patients may have lived through these ordinarily fatal diseases (such as pemphigus or lupus erythematosus) without benefit of the corticosteroids, it is certain that most have been kept alive by the corticosteroids for a sufficiently long period to permit these diseases to run their natural course to remission or cure. Similarly, we have the impression that there are patients with chronic and recurrent dermatoses who, after the prolonged use of corticosteroids, eventually have been able to discontinue the drug and remain free of the disease.

The careful and repeated examination of all patients receiving corticosteroids is an obligation of the physician, and the need for such care should be stressed to the patient. If in the regular search for possible adverse effects from the corticosteroids any complications occur, they should be managed promptly.

In our experience so-called "adrenal booster" shots of ACTH have not proved necessary while patients are receiving corticosteroids, except in isolated instances. We have found them to be of some benefit when patients on prolonged corticosteroid therapy complain of tiredness and a feeling of general weakness. This complaint is more likely to appear during the period when the dose is being reduced and, in particular, when it is reduced faster than the adrenal cortex can recuperate in order to produce its own corticosteroid hormones. In these instances ACTH given weekly or twice weekly for several weeks may be of benefit.

There is no question that the systemic administration of the corticosteroids has not only proved of benefit to victims of skin diseases but has revolutionized the practice of dermatology. For one thing hospitalization is required much less frequently than in the precorticosteroid days. Now that the effects and possible complications that may be produced by these compounds have become better known, it is possible to outline treatment with these hormones that may be carried out by the majority of patients on an ambulatory basis. In addition, once it has been ascertained that these hormones are effective in managing the particular disease and once the correct dosage schedule has been ascertained, it is possible to outline a course of therapy that the local family physician can administer, thus reducing the frequency of required visits to the specialist.

In opposition to the opinion that the long-term administration of corticosteroids is sometimes followed by addiction, by increased tolerance, or by a worsening of the disease (rebound phenomenon) when the corticosteroids are discontinued, we believe that:

(1) Addiction in the true sense of the word does not occur; patients on corticosteroids are not addicted or habituated to taking these drugs but, rather, are *dependent* upon them only as a means of keeping their disease under control. We have yet to see a patient who wanted to take corticosteroids for any reason other than to relieve his disease or its consequences.

(2) Once the effective therapeutic level of a corticosteroid has been ascertained for a particular disease, that dose will generally continue to keep the disease under control; in other words, increased tolerance does not occur. When a patient becomes worse without any change in the existing effective dose of the corticosteroid, it is probably the result of factors that would have acted even in the absence of corticosteroid therapy.

(3) At times, after certain dermatoses have been kept under control by the systemic administration of corticosteroids, there is a flare-up of the disease subsequent to the withdrawal of the drug that is worse than the disease had been at the time of instituting therapy. This so-called "rebound phenomenon"

usually can be avoided by very carefully adjusting the gradual reduction of the dose of the corticosteroid.

In the proper management of dermatological problems it is often necessary to do patch tests with various agents suspected of being the cause of the dermatitis under treatment. The question arises whether such patch tests will be valid or whether the results will be influenced if the tests are applied while the patient is receiving corticosteroids. As a result of investigations carried out in 1952 (Sulzberger *et al.*[4]), we were able to show that the results of patch tests applied while the patient is receiving corticosteroids may be accepted as valid provided the *standard* or orthodox patch test concentrations of the allergens are employed.

Furthermore, we do not believe that corticosteroids *alone* should be depended upon for the management of any of the dermatoses. In 1951, in our original publication on the use of oral cortisone in dermatological therapy (Sulzberger *et al.*[5]), we pointed out that the principal purposes for the systemic administration of corticosteroids were: (1) to get the patient through the crucial part of the acute phase of a dermatosis; (2) to obtain relief from the annoying, incapacitating, or dangerous symptoms and lesions of an acute or chronic dermatosis; (3) to afford relief while a dermatosis is investigated further; (4) to bring the dermatosis under control so that other forms of therapy can be used effectively; (5) to provide a temporary measure to aid the patient through a period of travel or to meet an emergency where he must feel well "at any cost"; and (6) to affect and maintain remissions in those diseases where the prognosis ordinarily is poor and where death may intervene.

Because of the importance of the adrenal cortex to life and because this gland is largely put to rest during the long-term administration of corticosteroids, we now customarily advise patients who are receiving long-term systemic corticosteroid therapy to carry with them at all times a card which gives information as follows.

Name: ....
Address: ....
I am currently receiving corticosteroids from
Dr. ....
Telephone: ....
Address: ....
In case of accident or other medical emergency, please notify him immediately.

We believe this is as important as the "dog tag" used by military personnel to give the wearer's blood type and other information. In view of the need to stimulate the adrenal cortex in the event of certain stressful situations such as surgery and dental extraction, we advise patients to notify us of such plans, in order to allow us to make arrangements to adjust the dosage of the corticosteroids so that the body can cope with the stress.

With the introduction of newer corticosteroids, it became evident that the complications resulting from their use were not only different in *degree*, but also different in *kind*. In the earlier days of cortisone, hydrocortisone, and then their delta analogues prednisone and prednisolone, it was only natural to select the corticosteroid that was less diabetogenic or ulcerogenic, and less likely to cause sodium retention and potassium loss. Experience with the more recent corticosteroids, such as methyl prednisolone, triamcinolone and, now, dexamethasone, has clearly shown that the complications differ in kind: for example, one tends to increase appetite, whereas another tends to reduce it, one occasionally produces muscle weakness, whereas the others do not, and some are inclined to cause insomnia or marked gain in weight while others do not. The selection of a particular corticosteroid for the management ot a given case is based on a knowledge of these differences that can determine the success or failure of treatment. Today, however, when selecting a corticosteroid, a third factor must be considered: the specificity of therapeutic effectiveness.

It is now obvious that certain diseases of the skin respond better to comparably smaller doses of one corticosteroid than another. This is a facet of the problem that will require additional years of study, as such differences in therapeutic response were first noted only recently in the use of triamcinolone in the management of psoriasis. Here, for the first time, an apparent specificity of therapeutic effectiveness was noted for triamcinolone, with which it is not unusual to see 16 mg. accomplish for psoriasis what ordinarily required 300 to 500 mg. of cortisone.[3, 6] Hence, it is not enough to speak of therapeutically equivalent doses of the corticosteroids in terms of milligram for milligram (as listed in TABLE 3); one must consider the disease to be treated before giving the *actual* therapeutically equivalent dose.

TABLE 3
THE APPROXIMATE THERAPEUTIC EQUIVALENTS OF 25 MG. OF CORTISONE

Steroid	mg.
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	3.5 to 4
Dexamethasone	0.75

While it is still not possible to predict the nature of the side effects or the degree of therapeutic effectiveness of a particular corticosteroid by examination of its chemical and structural formulas, the advances in this field of pharmaceutical and biological chemistry have been so rapid and the yield so great that the future holds promise for the synthesis of planned corticosteroids, each of which will have special properties known in advance to the chemist and the physician. In this way, it is hoped, therapy with corticosteroids will be carried out with the lowest possible incidence of serious complications.

The Topical Use of Corticosteroids

It has not been many years since cortisone was first used as a topical inunction for diseases of the skin. This compound, however, found very limited usefulness and is now relegated to instillation within the conjunctival sac. As the various derivatives of cortisone became available, several proved to be among the most effective topical medicaments ever to be introduced into the dermatologist's therapeutic armamentarium. The fact that newer compounds are regularly being synthesized and made available for topical use keeps this field of dermatological investigation an exciting one. It is thrilling to see sometimes stubborn dermatoses respond almost miraculously to these topical medications, and one's hopes for even better topical preparations are stimulated each time the newer compound proves more effective than the old.

It has now been approximately 7 years since we first used topical hydrocortisone in the management of various diseases of the skin. In our first paper, published in 1952,[7] Sulzberger and I reviewed 19 cases treated with hydrocortisone acetate ointment. Since that time our experience has been multiplied many times and in many ways. We have had an opportunity to treat many more diseases, to observe many more patients, and to evaluate many different preparations containing various corticosteroids.[8, 9] Wherever feasible we used the "simultaneous symmetrical paired-comparison" method[10] in order to evaluate new topical corticosteroid preparations. This method consisted of applying the test product to one involved site while the control preparation was applied simultaneously to a symmetrically involved site. As new preparations became available we were able to evaluate their effectiveness by the method of progressive comparison,[11] in which the new topical preparation was compared with the older previously evaluated products. These methods have permitted rapid and reasonably accurate conclusions concerning such aspects as the relative therapeutic effectiveness, undesirable side effects, and cosmetic acceptability of each newly introduced corticosteroid preparation.

The topical corticosteroids have proved beneficial in the management of many dermatoses, including: allergic eczematous contact-type dermatitis; anogenital pruritus; atopic dermatitis (including infantile eczema); dermatitis (for example, "idiopathic," contact, or atopic dermatitis of eyelids and perioral areas); distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe)*; eczema of nipples and areolae; exfoliative erythrodermas (some forms and areas); hand dermatitis (for example, primary irritant, "housewife's" eczema); intertrigo (inflammatory); lichen simplex chronicus; nummular eczema; otitis externa; psoriasiform dermatitis (some forms, especially of anogenital and intertriginous areas); seborrheic dermatitis (particularly of face); and miscellaneous eczematized and pruritic dermatoses.

The number of topical corticosteroid preparations available today is increasing at such a rate that a list compiled at this moment would be incomplete by the time it was read.

The topical corticosteroid preparations have many desirable properties, including "(1) great efficacy in the management of a wide variety of common dermatoses, often being rapidly effective even in small quantities; (2) ease of use and lack of stain, stink or sting when applied to the skin; (3) no reported allergic sensitization or allergic reactions; (4) no reported untoward systemic effects attributable to percutaneous absorption (with the exception of fluorohydrocortisone); (5) no regular increased resistance or habituation; and (6) compatibility with practically all other commonly used topical medicaments."[3]

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* Except in certain areas (for example, the penis) topical application is not as effective as systemic administration.

The contraindications to the topical use of these compounds are minimal. To date the only corticosteroid absorbed in sufficient quantity to produce systemic harm is fluorohydrocortisone which on occasion, has been shown to cause fluid retention on topical application. The topical use of corticosteroids for the management of thermal burns (Norman Kanof[17]) or in the treatment of cutaneous herpes simplex remains in question; it is definitely contraindicated for herpes simplex of the eye.

In addition, the corticosteroids used topically do not produce the undesirable side effects that may result from their use systemically; for example, topical application produces (1) no "lighting up" of latent internal infections; (2) no spreading of superficial cutaneous infections; (3) no acneiform eruptions; (4) no retardation of wound healing; and (5) no clinical evidence of absorption (except in the case of fluorohydrocortisone).

As each new corticosteroid has been made available for topical use, it has been compared (as stated above) by clinical trial with older preparations for which the most effective concentrations had been demonstrated. In this way the optimum therapeutic concentration of the newer preparations has been ascertained; these are given in TABLE 4.

TABLE 4

COMPARATIVE THERAPEUTIC CONCENTRATIONS OF TOPICAL PREPARATIONS

Steroid	Concentration (per cent)
Hydrocortisone	1.0
Fluorohydrocortisone	0.1
Hydrocortamate	0.5
Prednisolone	0.5
Triamcinolone acetonide	0.1*

* In our evaluations, the 0.1 per cent concentration of triamcinolone acetonide is, in many cases, more effective than 1 per cent hydrocortisone.

The numerous commercially available preparations of the various corticosteroids (made up in several concentrations in such vehicles as creams, ointments, lotions and, now, aerosol sprays) as well as combination products that contain a corticosteroid plus other active dermatological agents (such as tars, quinolines, and antipruritics) give the physician wide latitude for selection and prescription. While this is advantageous in many respects, it may also be detrimental in that the busy practitioner is likely to become confused when selecting a preparation for a particular patient. It is wiser to know a few products well and to use them to the exclusion of others, except where more effective compounds become available, as is currently the case.[12]

Every advantage should be taken of the effectiveness of topically applied corticosteroids, particularly when they are being given systemically also for the same disease. The effectiveness of the local inunction of a corticosteroid may result in sufficient improvement of the dermatitis to allow for considerable reduction of the systemic dose, thus reducing the possibility of undesirable effects. In a disease such as atopic dermatitis, it is frequently possible through the regular and continued use of the topical preparation to reduce slowly the dose of the systemic corticosteroid and, finally, to discontinue it.

The Intralesional Injection of Corticosteroids

There is increasing evidence that certain diseases of the skin, such as hypertrophic lichen planus, heavily lichenified circumscribed lichen simplex, alopecia areata and, occasionally, resistant plaques of psoriasis are benefited by the intracutaneous or subcutaneous injection of a suspension of hydrocortisone acetate,[3, 13, 14] prednisolone,[15] and, more recently, triamcinolone.[6] Tattooing has also been used to introduce the corticosteroid into the tissues.[16] The effective concentrations and preparations are those commercially available.

To bring this report up to date, I shall summarize our experiences with the latest of the anti-inflammatory steroids, dexamethasone. This review is based on results with twenty-one patients having skin diseases, who were treated at the Manhattan Veterans Administration Hospital, New York, N. Y., by Paraskevas Michaelides and Murray Kahn and by Marion B. Sulzberger in private practice. Of these, six received dexamethasone only, while the others had received another corticosteroid immediately prior to or following the dexamethasone. Six weeks is the longest period any patient was administered dexamethasone. Whenever possible, an attempt was made to find the equivalent therapeutic effective dose for dexamethasone by comparing it with the previously or subsequently established morbidistatic doses of other corticosteroids. Undesirable effects were carefully looked for and recorded. The dermatological disorders treated with dexamethasone are shown in TABLE 5.

TABLE 5
DERMATOLOGICAL DISORDERS TREATED WITH DEXAMETHASONE

Disorder	No. of cases
Psoriasis (plaque)	6
Psoriasis (exfoliative)	4
Atopic dermatitis	5
Hand eczema	2
Allergic eczematous contact dermatitis	1
Lichen planus (hypertrophic)	1
Nummular eczema	1
Dermatitis herpetiformis (?)	1

The results of therapy with this compound, in general, are not unlike those one would expect with such corticosteroids as methylprednisolone and triamcinolone, although the number of cases studied is yet too small to draw any definite conclusions regarding specificity of therapeutic effectiveness or of therapeutically effective doses. From our comparisons the range of equivalent effective doses of dexamethasone compared to triamcinolone is 0.45 to 0.9 mg.: 4 mg. The undesirable effects for short-term therapy were as follows. There was a gain in weight of from 2½ to 10 lb. in 9 patients, 7 of whom had a definite increase in appetite; 2 patients complained of abdominal distension, 2 of insomnia, and 2 of mild euphoria. A variety of minor complaints occurred in single instances only and 6 patients had no complaints.

Undoubtedly, dexamethasone will have its place among the various corticosteroids in the management of dermatological disorders; its exact therapeutic indications and contraindications remain to be ascertained, however.

Conclusion

It is evident that, as a group, the corticosteroids have done much to aid in the effective management of many dermatological disorders. This is obviously due to the extraordinary pharmacological and biochemical action of these compounds. However, effective management also results from the accumulation of a vast fund of clinical knowledge concerning these compounds, which aids the practitioner in their safe and successful use. The usefulness of the corticosteroids is increased further by the various modes by which they may be administered; that is, systemically (whether orally or parenterally), by topical application and, now, by intralesional injection. Furthermore, understanding the mechanism of action of these products is basic to the understanding of body function in both health and disease. Investigations in this field, therefore, by the chemist, biochemist, enzymologist, physiologist, physician, and many others is destined to continue. The discoveries of tomorrow may prove to be as phenomenal as the discovery of cortisone itself. Certainly it is our obligation as practicing physicians to know these compounds well and to use them wisely. We must also continue the clinical evaluation of the newer compounds as they become available. Only in this way may we find new corticosteroids with even greater beneficial effects and fewer undesirable ones.

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THE TREATMENT OF CHILDHOOD DERMATOSES WITH ANTI-INFLAMMATORY STEROIDS*

Leon Goldman

Department of Dermatology, College of Medicine, University of Cincinnati, and Cincinnati General Hospital and Children's Hospital, Cincinnati, Ohio

Some effort should be made critically to survey the field of corticosteroid therapy of childhood dermatoses despite the fact that it is perhaps of less importance than the other subjects presented in this review. The early reckless enthusiastic use of potent corticosteroid preparations for almost everything has abated somewhat. The position in pediatric practice is still not far from that characterized by the gloomy observation of Robert Good, Robert Vernier, and Richard Smith,[1] that "Few truly ill patients reach the diagnostic medical center without having had at least small amounts of cortisone or ACTH, and it is the extremely unusual patient who reaches the necropsy table without the benefit of ACTH, cortisone, or one of its analogues." Although, in the field of pediatric dermatology we deal with few truly ill patients, most of them have had some form of either systemic or, more fortunately, topical corticosteroid preparations. Gradually the absolute contraindication of corticosteroids in varicella has become well known, but the less dramatic-sounding indications and contraindications of the corticosteroid therapy of other cutaneous reactions of infancy and childhood are certainly not well known. The correct use of systemic and topical corticosteroid therapies is a necessity in the practice of modern pediatric dermatology.

A new type of clinical practice in dermatology and, incidentally, in dermatopathology, has arisen with the availability of corticosteroids. Patients are presented to the dermatologist with varying degrees of corticosteroid-induced inhibition of inflammation of their lesions, so that an already difficult field of diagnosis is even more confused. The confusion initiated by the incomplete therapy of the well-intentioned first observer of the patient is carried over also to the harassed dermatopathologist because there is also, in the microscopic picture, a different cytological and possibly histochemical response.

Another difficulty of this particular field of investigation derives from the rapid development of newer analogues. This impels the investigator to attempt to evaluate a new material critically, without anxiety and impatience, and yet rapidly. This dilemma, perhaps not warranted, is shared by the practitioner, who is bewildered by new claims and lost in the new nomenclature. It is actually only through long experience that we are able to estimate the long-range effect, the phenomenon of chronic toxicity. This applies especially to what is known conveniently as prolonged courses of a corticosteroid therapy, for it is there that the frequency and mechanisms of the unusual reactions peculiar to a specific analogue can be worked out.

It is lamentable that we still know little of the actual mechanisms of these powerful pharmacodynamic agents at the local or cellular level. Most of our

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energy is expended in the continued clinical investigation of the newer and the newest analogues. Even in this monograph too little is devoted to basic local mechanisms. It would seem that we who practice dermatology and who have exposed to our view an extensive and accessible organ should be able to study easily the local mechanisms of the action of corticosteroid at cellular level in human tissue. Local reactions in human tissue, however, differ from those in animal tissue, and the attempts made by my associates and me to study some phases of the local vascular component of the local corticosteroid reaction in the living skin of man has been completely frustrating.[2]

Before discussing particular experiences, I must add some additional reservations. First, in the majority of cases we deal with patients who are not ill, but who are healthy, miserable, very uncomfortable, and still very active. Second, responsibilities and obligations in a large university center require that clinical investigation be pursued in a much more varied and extensive way than would be described reservedly as routine clinical practice. However, when I observe the recklessness with which these potent agents are prescribed, I wonder if the limitations of routine practice are really in force. Sometimes cost is the only deterrent, but this does not hold for pediatric dermatology, except insofar as the topical preparations are concerned. Since the action of corticosteroids is assumed to be universally and nonspecifically anti-inflammatory, it is assumed that it no longer is necessary to take the trouble of making a diagnosis; this was also the view in the early days of antibiotics, and the recent renaissance of bacteriology has established the fallaciousness of it. If one does not know the disease, one cannot presume to treat it effectively with corticosteroids.

In brief, for pediatric dermatology, we must consider two general courses of treatment: one is the so-called short, usually intensive course; the other is the prolonged course, which may or may not be intensive. In our experience, from a clinical aspect, brief courses may be assumed to include those for which the systemic corticosteroid is used for less than one month. This arbitrary division into clinical courses of treatment should not encourage a feeling of security, for reactions have been found in the short courses of treatment also. However, in the field of dermatology the acute explosive reactions for which the corticosteroids are required are much more numerous than those for which corticosteroids may be required for prolonged therapy. The dosage requirements will be considered below.

General Indications for Systemic Therapy

The diseases for which I have used the corticosteroids are (1) uncommon lupus erythematosus syndrome in infancy and early childhood; (2) the more common dermatomyositis; (3) the intractable infantile eczema-atopic dermatitis group; (4) the severe drug reaction including the Stevens-Johnson type of syndrome; (5) severe urticaria and serum sickness; (6) the allergic purpuras; (7) Leiner's disease and other "idiopathic" erythrodermas; (8) Letterer-Siwe disease and the cutaneous manifestations of lymphoma that are uncommon in childhood; (9) the vague group of persistent erythema multiforme reactions of unknown etiology, but with suspected (unproved) rheumatic group relationships; (10) the severe contact dermatitis, especially the very severe plant dermatitis from poison ivy and poison oak; (11) Brazilian pemphigus in children, the rare group in which, with Mario Fonzari (personal communication) we have been interested, and which is important because pemphigus in the adult is one of the prime requirements for corticosteroid therapy; (12) severe bites from arthropods; and (13) miscellaneous afflictions (Charles Dennie's "therapy of panic") such as psoriasis, epidermolysis bullosa, urticaria pigmentosa, and pityriasis rubra pilaris.

As one surveys this group, there may be objections to vague terminology such as "severe," "intractable," and "persistent." These qualifying terms are obvious but feeble safeguards used to prevent their indiscriminate use in describing the commoner and less severe reactions of the particular group. Such restrictive qualifications may not always be evident in medical advertisements. One sees also how closely this group is related to the dermatoses of the adult.[3]

This review, then, presents a detailed list, of necessity brief, although each indication should raise questions and controversy. No question about corticosteroids is more important than that famous one first asked 10 years ago: If I start corticosteroid therapy, when do I plan to stop it? Ten years ago, if one was unable to answer this, it was assumed that one would not start such therapy. The first question is followed with a second: If there are reactions, will these be worse than the disease I am to treat? Again, for routine clinical practice, the cost aspect of these recent analogues is another practical question that must still be asked by the family before especially long-term courses are planned.

We must continue to ask questions concerning specific features of those diseases that we have treated with corticosteroids:

(1) Should we continue corticosteroids in dermatomyositis if the child develops a chronic type?

(2) If the so-called reaction of neurodermatitis (not prevented by early corticosteroid therapy) develops extensively in atopic dermatitis, should we use systemic corticosteroids?

(3) In the puzzling group of "idiopathic" chronic erythema multiforme reactions with fever, discomfort, and lack of response to antibiotics and acetylsalicylic acid, should we use brief courses of corticosteroids?

Severe psoriasis in children has occupied our interest for a number of years. I have observed the effect of corticosteroids on improvement and relapse and the emotional state of the child and, at present, would use it hesitantly, in the hope that it will require only a brief course in very severe disseminated psoriasis.

Many of these children are ambulatory patients, and this is a factor that must be considered, for, without the security of the hospital environment, complications may develop more easily.

Dexamethasone Therapy

The question of what corticosteroid should be preferred is obviously of interest. In the early days of steroid therapy, most of our experience has been with infants and children treated with prednisone and prednisolone; use of the dexamethasones was begun only recently. At present, for investigative purposes and for ordinary clinical practice, treatment with systemic corticosteroid therapy in children is done entirely with the dexamethasones, which are highly effective in the treatment of dermatoses of infancy and childhood for which corticosteroids are indicated. It has not been necessary to change the type of steroid when there was no response. In the adult, occasionally, better results are achieved in such diseases as pemphigus, lichen planus, or psoriasis by a change of type of corticosteroid. Where there is no question of inadequate dosage or of some reaction peculiar to the analogue, such a response may be idiosyncratic on the part of the particular patient rather than a reflection of a prejudice of the observer. If the shift to another corticosteroid is made because of an undesirable reaction, the physician must be aware that the reaction may be of a type produced by all corticosteroids.

Dosage

It has been our opinion since the early days of corticosteroid therapy, that the dosage of corticosteroids must be adapted to the needs of each patient. Extreme examples of this occur, of course, with the severe Stevens-Johnson syndrome or severe crisis of lupus erythematosus. Where very large doses may be required, even for such an ailment as severe poison ivy dermatitis, the initial doses must be high to attempt to prevent the rapid development of severe bullous reaction. Where there are many lesions with much inflammation, the upper range of dosage should be preferred. Most of our patients are relatively healthy children and can tolerate relatively high dosages. As a rule, the initial dosages should be high for 3 to 4 days or less. In a disease ordinarily controlled by corticosteroids, if there is no beginning response, the dosage may be inadequate. At times this response may be evident in the prevention of new lesions, or in the prevention of progress of recent lesions, rather than in the evident clearing of a huge bullous lesion. Here clinical experience is required to evaluate the characteristics of an early response. How accurate must the dosage be? Shall we consider, for pediatric dermatology, milligrams per kilogram per day, milligrams per square meter of body surface, or simply general age groups such as newborn, infant, school child, and prepuberty child? With Harry Shirkey, at the Children's Hospital, we are attempting to determine the value of expressing dosage according to the ratio of the area of severe skin lesions to the area of uninvolved skin. We shall attempt to compare these dosages with those estimated for skin diseases of the same severity in the usual age groups. With due regard for the severity of the disease and the average body size, we suggest as average initial dexamethasone therapy for the general age group types:

Age group	Dosage mg.
To 1 year	0.15–0.25
2 to 5 years	0.50–0.75
Young school child	0.75–1.50
Prepuberty (unless small)	1.50–3.0

There may be many objections as to the value of such expediency, but these can be answered by using the average initial dosage as shown, and by then modifying the dosage to suit the individual case. Daily administration of the drug is divided into 3 to 4 doses, given after meals or with milk or orange juice.

Then, as indicated above, there should be a gradual reduction of dosage to determine for each patient the minimum effective daily dosage. The usual precautions in regard to gradual diminishing of dose before cessation of therapy also continue. Occasionally, in poison ivy dermatitis we have observed urticaria after the healing of the bullous eruption. If this occurs, small daily doses may be used for 5 to 7 days after the subsidence of the dermatitis. In order to reduce the duration of corticosteroid therapy in such a common disorder as severe poison ivy dermatitis we recommend discontinuance of therapy after the dermatitis has well subsided. As Albert Kligman[3] has indicated, poison ivy urticaria is rare and is limited to very sensitive patients. Unlike those in his patients, our urticarial reactions have come after the acute episode has subsided.

The question of dosage is also important in deciding the efficacy of corticosteroids. Before one concludes that corticosteroids are ineffective, an adequate dosage must have been provided over an adequate period of time. For example, for an acute reaction of severe hypersensitivity an arbitrary period of at least 3 to 4 days with an adequate dosage, which may be 2 or 3 times the recommended dosage, may be required to decide that corticosteroid therapy is of no value.

Another feature of dermatological corticosteroid therapeutics involves the use of intravenous corticosteroids. The initial success of intravenous corticotropin in dermatology gave rise to the consideration of intravenous administration of corticosteroids to achieve a rapid effect. For this technique we have used prednisolone hemisuccinate chiefly. In our experience this has been effective in severe lupus erythematosus, severe drug eruptions, Stevens-Johnson syndrome, severe arthropod bite reaction, and anaphylactic reactions. We have not had sufficient experience with intramuscular corticosteroid therapy to evaluate it.

Another phase of intravenous corticosteroid therapy has been studied by Lawrence Goldberg in our department. He has worked with intravenous 6-methylprednisolone and has shown that, where corticosteroid therapy is indicated in dermatology, frequent intravenous use provides the desired anti-inflammatory activity rapidly and without the usual reactions, especially of electrolyte disturbances or Cushinglike syndrome. The mechanism of this technique of repeated intravenous administration has not been determined, and the critical details have not been completed. Whether the effect is due to the rapid availability of corticosteroid, without retention in tissue, is not known; we have not yet used intravenous dexamethasone.

Reactions

The question of reaction to corticosteroids always must be considered. In spite of the great temptation to use corticosteroids, where the reactions may be more severe than the need for the corticosteroid therapy, they should not be used in routine clinical practice.

Much has been said about the different types of reactions to corticosteroids. Although children are not immune to these reactions, in our experience they have shown fewer and less severe reactions than adults; reactions with the newer analogues have been even less serious. Clark West (personal communication) at the Children's Hospital, has had the same experience. The reactions may vary; in our experience with well children the most frequent reaction has been secondary infection, chiefly in the skin and less commonly in the respiratory system and gastrointestinal tract. This is not surprising when we see how active a child may be and how dirty his skin may become. Most of the infections have been by *staphylococcus*; these do not necessarily include the coagulase-positive phage-type resistant groups. Occasionally yeasts have been involved, including *Candida albicans*. We are in an area where histoplasmosis is endemic; together with mycologist Jan Schwarz, who is interested in histoplasmosis, we have become acutely aware of the possibility of the activation of histoplasmosis as a result of our prolonged corticosteroid-antibiotic routines. Thus far the only case we have observed of proved histoplasmosis associated with this type of therapy has been that reported by Harry Fox (personal communication). This factor of secondary infection has been present even in the brief courses of therapy. The early recognition of secondary infection of the skin is simple and requires immediate attention to both local treatment of the skin and associated antibiotic therapy. We do not recommend routine prophylactic antibiotic therapy in routine systemic corticosteroid therapy in children unless the patient is infected. In the hospital, using the usual aids of temperature, white count, and repeated blood culture to follow the course of the patient, we have not observed virus infections such as herpes zoster or varicella as complications in children. The severe reactions associated with varicella have been noted above; we are aware of the possibility that viral infections may flare up and have not observed such in our study. We have not used steroids in generalized herpetic dermatitis caused by the herpes simplex virus and superimposed on an atopic dermatitis.

Gastrointestinal reactions to corticosteroids are uncommon in children. In our studies with prednisone, we had only one child who had severe gastric pain and discomfort associated with the moderate therapy administered for a severe and recurrent poison ivy dermatitis. This child had also an atopic dermatitis and asthma. No gastric ulcer developed. In another child (one with a recently proved and healed gastric ulcer) prednisone in moderate doses with EXul was used without any bad effect. Joseph Shaiken[4] has indicated recently that gastric and duodenal ulcers are more common in children than has been supposed. In our dexamethasone series of only 46 children and 208 adults, no gastrointestinal reactions have been observed, nor have we observed any so-called postcorticosteroid diarrhea crisis in our infants. Weight gain and appetite improvement, of course, have been recorded for dexamethasone as it has for the other analogues. We have had one mild case of insomnia in an older child. This reaction has been observed in the adult and we have attempted to give the last doses earlier and to use perphenazine (Trilafon) at bedtime. We have observed also occasional cramping pains in the arms and legs of adults treated with dexamethasone, but this has not been observed in children. There has been occasional skin hemorrhage, but none has occurred in the dexamethasone group.

The emotional reactions associated with corticosteroid therapy have also been of some interest to us through our associated psychiatric service for psychosomatic dermatology. The atopic child, already subject to a degree of emotional disturbance, has been followed by Jay Shanon (personal communication) with EEG studies before, during, and after corticosteroid therapy to determine whether we can detect early cerebral reactions from corticosteroids and perhaps prevent development of actual psychotic phases. Excitability, depression, and fatigue have been some of the reactions noted in these children. No major psychoses have developed in this disturbed group. When we have encountered reactions of fatigue, insomnia, or excitability, we have discontinued the corticosteroids. In our study with dexamethasone, the compound has been given to children of prepuberty age with severe atopic dermatitis, and we have seen obvious emotional disturbances. There was 1 sudden death with negative autopsy findings in an infant treated several years ago with hydrocortisone for epidermolysis bullosa. Early prepuberty acne and seborrhea has been observed in older children, but not in infants. One case of hypothyroidism developed in a girl of 10 treated for an acute disseminated lupus erythematosus on prolonged courses of corticosteroid therapy and observed for 6 years. The inference was that this was associated with the corticosteroid therapy. In the prolonged courses of treatment, especially in dermatomyositis, we have attempted to use Norethandrolone-type preparations such as Nilevar to prevent so-called corticosteroid catabolism. We have not used such therapy with corticosteroids in malnourished infants.

West, at the Children's Hospital, has observed one brief post-ACTH psychosis from excessive dosage. No true growth difficulties of children were found although, when intensive courses of corticosteroids were discontinued, as in nephroses, the children appeared to "spurt ahead." No gastric ulcers were found and there was no unmasking of latent or familial diabetes. In brief, West indicates that with corticosteroid therapy in children he "used to worry," but does not now, although "perhaps that is wrong, too."

Topical Corticosteroids

Topical corticosteroids, perhaps the most important phase of corticosteroid therapy in children, will be discussed very little, as much has already been done in this field. The question today appears to be, simply, which of the many available ones shall be used. We agree with Sulzberger *et al.*[5] that hydrocortisone, prednisolone, and ethamicort are the "corticosteroids in most widespread use for topical dermatological therapy." The best available list of this huge complicated group of topical corticosteroids is reported by these authors.

We have used the highly effective fludrocortisone in children without resultant weight gain or evident electrolyte disturbance. To force this, we used even total body inunction in three infants. In actual practice it is best to become familiar with the effects of some specific ointment and lotion and to learn to use them correctly. The parents must be warned in advance about the initial and continued expense of topical corticosteroids. Where one uses topical corticosteroid for larger areas, the lotions are preferred; the drier the skin the heavier the grease base required. At least with the initial therapy, the highest concentration available should be used. We have had limited experience with topical dexamethasone creams and lotions. Although these are effective, we have not had sufficient experience to determine the minimum effective concentration. For children, the antibiotic combinations are required. Fortunately the neomycin sensitivity index in children is small. Such chemotherapeutic agents as Vioform, Sterosan, or Diodoquin also may be added for use with children to prevent infection. These medications also may have some antieczematogenic quality. For children, also, especially in the secondary infection of diaper dermatitis and flexural areas, yeast infections may develop together with those caused by the staphylococci (including the famed antibiotic-resistant form). Therefore, the addition of some form of Nystatin, such as Myconef, is also recommended. The reactions to topical corticosteroid medications have included chiefly secondary infection and sensitivity to neomycin and methylcellulose. In areas of thickened skin, tar combinations are of more value than the topical corticosteroids alone.

Local Intralesional Injections

Local injection of the newer analogues of hydrocortisone is occasionally used in pediatric dermatology. It is of relatively minor importance compared to other forms of therapy. These injections may be employed in hypertrophic scarring and keloids, nodular urticaria pigmentosa, small persistent facial patches of discoid lupus erythematosus, psoriasis, early neurodermatitis (especially about the ankles in children), granuloma annulare, and localized xanthogranuloma. We have used chiefly hydrocortisone, t-butyl acetate, and hydeltra-t-butyl acetate. The injections are made with a 27-gauge needle. In some instances we have used the Hypospray Jet injection apparatus. Recently we have been using dexamethasone phosphate for local injection in both children and adults.

Summary

In modern pediatric dermatological practice, systemic corticosteroids are often useful and, occasionally, may be absolutely necessary. Even after 10 years, these newer and less dangerous analogues are still recognized as potent pharmacodynamic agents. In the severe explosive skin reactions of infancy and childhood, corticosteroids may be given for brief intensive courses. Reactions to the newer analogues are not frequent in children, but reactions may occur with the brief course as well as with the intensive courses. The commonest reaction in childhood is one of secondary infection. When the reaction may be more severe than the disorder, the corticosteroid should not be employed. The dexamethasones are highly effective for those dermatoses in children for which corticosteroid therapy is indicated. Topical corticosteroids are used more extensively than systemic corticosteroids in infancy and childhood. In some rarer instances, intralesional injections of corticosteroids may be used.

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Discussion of the Paper

Question: Compared to those of us who are studying the use of corticosteroids in the rheumatoid and rheumatic field and for such diseases as nephrosis, the dermatologists are really more suited to evaluate these agents because they can observe the changes taking place.

Witten brought out several points that coincide with our way of thinking and our experience. One of these is that the corticosteroids may be given in amounts that will cause some minor degree of side effects. We feel that side effects of this degree are not of a serious nature and, that even if dosages required to suppress the disease induce some of them, these dosages should be given. I believe Goldman said that he gave almost as much corticosteroids as possible without causing side effects. We have not been able to escape side effects, and this so-called "steroid excess" cannot be completely obviated when one wishes to suppress a certain disease. I wonder if Witten and Goldman would care to say anything to reconcile this difference.

Another point concerns the withdrawal of steroids. We are extremely anxious about withdrawal in children. We have seen children die within a very short time after the cessation of steroids in such a case as acute infection, and we wholeheartedly favor the carrying of an "insulin-type" card. We routinely warn parents that their children are on corticosteroids, and inform them of the possible consequences that may follow development of an intercurrent infection.

Question: I hesitate to bring up the problem of allergic reactions to the corticosteroids since they occur so uncommonly, but may I ask whether any serious allergic reactions from the injection of ACTH have been seen. Recently I saw a man die in constitutional shock; the presumption of death following autopsy was that it was probably the result of a reaction to intramuscularly administered ACTH. Of course, it is just a presumption. We could not prove it, since the pathologist said that one cannot prove death due to allergy. However, I wonder if others have had a similar experience.

Victor H. Witten: I think that Goldman will discuss the differences of opinion regarding corticosteroid dosage; however, I do not feel that any differences of opinion really exist. Regarding the well known occurrence of allergic reactions to ACTH, they are probably due to animal protein. In the early stages of ACTH use we attempted to ascertain the cause of these reactions (seen in only a few patients) by doing tests in one patient with such proteins as those of beef and pork. We have not seen such reactions lately either because we use ACTH only in the most unusual instances, when we are tapering off long-term corticosteroids, or because more highly purified extracts are being manufactured. We are of the school that feels that ACTH is not necessary, provided one decreases the corticosteroid dose in small decrements during a sufficiently long period.

Leon Goldman: In regard to the question on dosage, I do not advocate continued large dosages. Large doses may be employed initially, however, with little or no danger of side effects. For example, if one is fortunate to see poison ivy dermatitis in the early stage of development, one gives large dosages for a very brief period of time. Large doses are certainly not continued, because reactions are proportional to the dosage. The ideal therapy program is the minimal effective daily dosage.

Concerning the withdrawal of corticosteroids in children, the withdrawal schedule is carefully worked out, and the child is constantly observed. We prefer that, during the period of withdrawal, the child be kept off the playing field and in the house in order that fatigue resulting from physical activity may not be confused with possible fatigue occurring during steroid withdrawal.

In regard to allergic reactions to ACTH: they do, of course, occur, even to fatal anaphylaxis. Allergic reactions have also been reported as having followed the local injection of corticosteroids. I do not know whether it has been noted very much in intra-articular injections, but we have seen reactions to the suspension, and it has been proved to be due to the presence of methylcellulose. I know of a very severe hemorrhagic reaction following the local injection of a suspension of hydrocortisone, and I think the testing showed that it was due to methylcellulose. Allergy to the corticosteroid itself has not been demonstrated clinically, although antibodies may be produced.

ADRENOCORTICOSTEROIDS IN THE TREATMENT OF TUBERCULOSIS IN CHILDREN

Margaret H. D. Smith
Department of Pediatrics, New York University-Bellevue Medical Center, New York, N. Y.

This brief report concerning the use of steroids in the treatment of tuberculosis in children results from a study now in progress on the Tuberculosis Ward of the Children's Medical Service at Bellevue Hospital. Progress reports have already been made before several organizations, including the American Trudeau Society,[1] Saranac, N. Y., and parts of the study have been discussed and reported in the journal *Pediatrics*.[2, 3] It will be several months before the final report is prepared.

The dangers inherent in the use of adrenocorticosteroids during acute infections have been pointed out by many authors, but surprisingly few have drawn attention to the advantages to be gained by using steroids together with antibacterial drugs. A few observations on the course of experimental pyogenic infections where both steroids and chemotherapeutic agents were used suggested that such combined treatment might not only be safe but advantageous. These principles, applied to the management of typhoid fever, pneumococcal pneumonia, brucellosis, and other severe infections, have yielded excellent results.[4] In the case of tuberculosis, animal experiments of Bacos and Smith,[5] Karlson and Gainer,[6] and others provided encouragement. Lurie and his coworkers,[7] and also Ebert,[8] showed in beautiful experiments that, in laboratory infections in rabbits, cortisone reduces the fragility of the capillaries and the inflammatory response to tuberculin, thereby diminishing the extent of necrosis and later caseation. There is also evidence that cortisone inhibits fibroblastic proliferation and, consequently, the development of granulation tissue and fibrosis.

By attempting to take advantage of the above actions of steroids and by coupling them with bactericidal drugs, numerous clinicians, particularly in Europe, have treated 4 general groups of tuberculous patients with combined steroid antimicrobial therapy. The 4 groups comprised patients with (1) tuberculosis of the serous membranes, including meningitis, pericarditis, and pleurisy; (2) tuberculous adenopathy, both mediastinal and cervical; (3) far advanced pulmonary tuberculosis; and (4) drug reactions with hypersensitivity to streptomycin, PAS, or both. While the benefits in some types of tuberculosis are doubtful, there seems to be general agreement that tuberculosis of the serous membranes (meningeal, pericardial, and pleural) is in general favorably affected by steroids. It is in this type of disease, especially where the lesion is early and predominantly inflammatory in character, that one might expect the best results. On the other hand, where the process is of long standing and where fibrosis is to be expected, little if any benefit may be expected from the use of steroids.

The experience of my associates and myself during a 2-year period includes a study of 58 tuberculous children treated with steroids. Others have received steroids since then or are now under treatment. While it is still premature to evaluate the results of treatment in these recent patients, we can already say that they are responding in every way as did the previous ones.

The 58 patients are grouped according to their condition: pleural effusions, 7; tuberculous meningitis, 5; endobronchial tuberculosis with segmental lesions, 41; miliary tuberculosis, 3; axillary adenitis, 1; and chronic pulmonary tuberculosis with asthma, 1.

The patients with pleural effusions were children between the ages of 2 and 11. Six were admitted within the first 10 days of their illness; the seventh was referred to us from another hospital because of unsatisfactory course, and the interval before adequate therapy in this case was 4 months. All patients were tuberculin-positive and, in all, the diagnosis was established beyond reasonable doubt by cultures positive for *Mycobacterium tuberculosis* obtained from pleural or gastric fluid or, in one case, by a caseating granuloma present on a pleural biopsy specimen.

Treatment consisted of large doses of INH (20 mg./kg. of body weight), PAS (0.5 gm./kg. body weight), and Meticorten, started a few hours after the antituberculous drug in doses of 0.5 to 1.0 mg./kg. of body weight every 24 hours for at least 1 month. In 4 patients the course of the illness was smooth, with disappearance of the effusion within no more than 2 weeks. A fifth patient, actually the first in the series, received hydrocortisone for 7 days; her fever fell promptly and the effusion cleared, only to recur 48 hours later. A second course of hydrocortisone was followed by an equally prompt clinical response and no recurrence. In 1 other patient a relapse occurred at the time of transfer from one ward to another, when steroid administration was inadvertently interrupted. The latter 2 patients were of particular interest in that they served, in a sense, as their own controls, with recurrence of signs and symptoms at the time of temporary interruption of the steroid; the antituberculous drugs were administered without interruption.

A seventh patient, suffering from fibrocaseous pleurisy at the time of admission to our hospital, recovered very slowly after 4 months of treatment; in his case adrenocorticosteroid therapy appeared to exert no effect on the course of the disease.

For *tuberculous meningitis*, results reported by authors in several countries (namely Italy, France, and South Africa) leave little doubt that steroids exert a definitely beneficial effect on the course of the disease. A comparative series of patients observed in South Africa and reported by Heymann[9] suggests that, while the mortality is lower, the most striking effect is on the incidence of sequelae in the survivors. Observations on our 5 patients lead us to believe that this is due to the rapid fall in intracranial pressure, which occurred after administration of the steroids. Our series is too small to permit statistical evaluation: 1 patient, admitted after 3 months of inadequate therapy at another hospital, later died; 1 survived with sequelae; and 3 others are convalescing satisfactorily.

Of great interest to us are patients with adenitis, particularly with the kind of hilar adenitis that develops in the course of most cases of primary infection by the respiratory route. These enlarged nodes, by their very size, often compress the adjacent bronchus, rupture through it, and cause "collapse-consolidation" lesions; they may go on to caseation and calcification. Several French authors have shown that steroids may cause rapid shrinkage of these lesions, with consequent reaeration of the corresponding bronchus. Evaluation of improvement is difficult; our experience has not included a controlled series, but only consecutive cases, *all* treated with steroids. We have found, as have the French, that approximately two of three patients respond quickly and well, as judged both by clearing of the segmental shadow on X ray and by clearing of the endobronchial lesion observable by bronchoscopy. No patient developed a perforation of a bronchus while being administered steroids. Cessation of steroid administration was sometimes followed by a "rebound" phenomenon. With the thought that the very small dose of 0.5 mg./kg./24 hours (used at first) might not be optimal, we increased it to 1.0 mg./kg., and the incidence of rebounds seemed lower. At present we are in the midst of a series in which patients receive the same dose for a somewhat longer period. At the moment there appears to be a slight further drop in the occurrence of rebound phenomena. However, if the pretracheal and peribronchial nodes are so enlarged as to cause wheezing and acute respiratory obstruction, the steroids produce remarkable improvement, as we observed in 5 patients. In our 1 case of axillary adenitis, administration of steroids was followed by prompt subsidence.

In children with miliary tuberculosis we have not been favorably impressed by the beneficial results of steroid administration. X-ray clearing seems no more rapid, although others treating both children and adults have noted quick relief from cyanosis and dyspnea in patients with severe miliary tuberculosis. Under such circumstances we, too, would have no hesitation in using steroids.

Our entire experience has been with the use of Meticorten, and the dosage regime used now is as follows: 1 mg./kg./24 hours, divided into 2 doses and given for 6 weeks; one half the dosage during the second period of treatment, lasting 2 weeks; and 0.25 mg./kg./day during the final 2-week period. Throughout this course of treatment and for months afterward, isonicotinic acid hydrazide is administered in a dosage of 20 mg./kg. daily and sodium para-aminosalicylic acid, 0.5 gm./kg. daily; only patients with miliary or meningeal tuberculosis receive streptomycin in addition.

In summary, on the basis of experience with 58 tuberculous children to whom steroids were administered in addition to specific antituberculous therapy, we find in certain cases definite advantages in combining anti-inflammatory and antibacterial therapy in the treatment of tuberculosis in children.

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Discussion of the Paper

SAMUEL C. BUKANTZ (*Jewish National Home for Asthmatic Children, and Children's Asthma Research Institute and Hospital, Denver, Colo.*): I ask a question that may bear a little obliquely on this presentation, but may prove of interest to those of us who have to deal with children and steroids. Can Smith tell us how she feels about the use of steroids in tuberculin-positive children? Is there any change in the size of the tuberculin-positive reaction in children who have been treated with steroids? What tuberculin-test technique would she recommend?

MARGARET H. D. SMITH: As far as the use of steroids in tuberculin-positive children is concerned, our rule at Bellevue is that any child with a positive tuberculin test who is to be treated with steroids for any reason should be given INH and PAS in therapeutic doses. There is excellent evidence that steroids do activate tuberculous disease in a considerable percentage of cases; since the patient is a child, the infection is, of course, relatively recent and therefore susceptible to activation. In children there are even fewer drawbacks to antituberculous therapy than there are in adults, so that we see no reason for not giving INH and PAS in full doses for as long as the patient is on steroids and probably for two or three months beyond that time.

In connection with the size of the tuberculin reaction in patients on steroid therapy, last year we tuberculin-tested a large group of patients on steroid therapy; we measured the size of the reactions daily, and found that it was a little smaller (perhaps by 10 or 20 per cent) in the children on our dose of steroids, which is a small dose compared to that administered by some physicians. In addition, the reaction disappeared a little more rapidly in the steroid-treated children than it did in the nonsteroid controls. No one who had had a positive reaction prior to steroids demonstrated a negative reaction while on steroids.

With regard to the type of tuberculin test, we always use an intradermal one, either with old tuberculin or with PPD. Our study last year was done with PPD-S supplied by the United States Public Health Service; this is ideal when obtainable.

QUESTION: Do you not encounter the problem of drug resistance in these children after 2 or 3 weeks of INH dosage?

SMITH: The situation in children is entirely different from that in adults. In general, however, one can say now (although the situation may be different in 10 years) that the problem of drug resistance (that is, resistance to INH and PAS) is, for all practical purposes, nonexistent in children and does not develop unless, perhaps, with a 10- or 12-year-old with extensive cavitary disease who responds like an adult. As compared with adults, there are not enough tubercle bacilli in children to promote the development of resistance, nor are the conditions for multiplication of bacilli as favorable.

DEXAMETHASONE IN OPHTHALMIC DISORDERS

Dan M. Gordon
New York Hospital-Cornell Medical Center, New York, N. Y.

Dexamethasone, a new adrenocorticosteroid, has been used since May 1958 in the treatment of a group of 66 patients with various inflammatory intraocular conditions. Our preliminary observations indicate that the synthesis of dexamethasone, obtained by addition of a methyl radical at carbon 16 and a fluorine atom at carbon 9 of the prednisolone structure, constitutes a definite advance in the field of corticosteroid-responsive ocular conditions.

According to early reports, dexamethasone is said to have approximately 6 times the potency of prednisone or prednisolone and 30 times that of cortisone.[1,2] Certain of the undesirable side effects seen with the earlier corticosteroids seem to be greatly decreased in incidence with dexamethasone.[3,4]

Clinical Evaluation

Dexamethasone was given to 66 patients with corticosteroid-responsive ocular conditions. The therapeutic regimen was essentially the same in all patients; that is, relatively high initial dosages (up to 3.5 to 4.5 mg.) were used. These dosages were discontinued at the earliest possible time in acute conditions, and gradually decreased to maintenance levels in chronic processes. If the patient exhibited any sign of a flare-up, dosage was immediately increased until the exacerbation was under control.

Uveitis. Five patients with acute iridocyclitis were treated with 1.5 to 3.0 mg. dexamethasone daily, for periods of from 5 days to 6 weeks. All 5 responded satisfactorily, with no side effects from the corticosteroid. In 1 of these cases, the uveitis followed trauma; there was no delay in the absorption of the accompanying hyphema.

Seven patients with recurrent anterior uveitis received dexamethasone in initial dosages of 3 mg. daily in divided doses. The response was highly satisfactory in all 7 cases; therapy was given for as long as 10 weeks.

Three patients with acute choroiditis responded well to essentially the same dosage regimen as that given to the preceding 7 cases. One required treatment with dexamethasone for 6 weeks, and another for 3 months. The third patient has had a fluctuating response, and the result must be considered equivocal at this time. Six patients with recurrent choroiditis, including 2 with choroiditis juxtapapillaris, responded dramatically to dexamethasone. In our experience, choroiditis juxtapapillaris is usually a difficult disease to manage. The duration of therapy is generally longer than that required in lesions of similar appearance located in other areas of the choroid.

Four patients with long-standing chronic choroiditis received dexamethasone. In 1, vision was 8/200 at the initial examination, and the density of the vitreous membranes prevented examination of fundus detail. This patient failed to respond after a trial period of 4 mg. dexamethasone daily for 2 months. Another patient responded initially with improvement of vision from 20/80 to 20/50 and then fluctuated irregularly; this patient had previously been on triamcinolone with a similar response and had then developed marked muscle weakness. After approximately 1 month on dexamethasone he again complained of muscle weakness; however, this reaction was milder and disappeared gradually. When the patient appeared to be responding satisfactorily, he developed new lesions and, despite all efforts, lost his vision in the affected eye.

A patient with severe, acute retinal periarteritis and generalized uveitis and 20/80 vision presented a hazy vitreous. He had been placed on 30 mg. prednisone daily when first seen. Transfer to 3 mg. dexamethasone daily, produced an excellent response within 1 week. The period of treatment was 10 weeks, and vision has improved to 20/20.

Twenty patients with chronic generalized uveitis were treated with dexamethasone. The uveitis was brought under excellent control in 18 of these cases; 1 patient developed marked edema, requiring transfer to an alternate corticoid; another must be considered a failure at this time. Five patients developed edema in varying degrees. Water retention was controlled in most cases by administration of 500 mg. of chlorothiazide once or twice daily or every other day. In the more severe reactions, intramuscular injection of 2 cc. of mercury every week or every other week proved of great value.

It is noteworthy that the intensity and duration of treatment in chronic uveitis exceed those seen in most medical diseases, and that the probability of eliciting side effects is thus greatly increased.

Neuritis. A patient with an acute generalized uveitis and bilateral optic neuritis responded extremely well to dexamethasone, administered for one month.

A female patient with retrobulbar neuritis, whose vision had been reduced to the perception of hand movement, responded to dexamethasone within 48 hours with marked improvement of vision and fields. Treatment was continued for approximately 2 weeks, when vision became normal. After treatment was discontinued at the patient's request, there was a prompt relapse of vision to approximately 20/50. When dexamethasone was reinstituted, there was again immediate and continued improvement. Treatment was continued for an additional 6 weeks at lower dosage.

A patient with a chronic optic neuritis of 1 year's duration in 1 eye and of several month's duration in the other is responding well to dexamethasone, with marked improvement in vision and reduction of edema within the nerve.

A patient who underwent a 9-mm. corneal transplant had an intense postoperative reaction, including a severe uveitis; he was successfully managed on dexamethasone, administered for more than 2 months.

A patient with Coats' disease was treated for 6 weeks with dexamethasone. There was no improvement in his condition; none had been expected. Two other patients with burned-out chronic uveitis were treated for approximately 3 months, with no improvement in vision.

A male patient with Behcet's syndrome, who had failed previously on prednisone and who had been managed only on massive doses of ACTH (120 to 200 U. daily), responded in the same degree to 4 mg. dexamethasone daily.

A patient with macular degeneration, consisting of white plaques and edema with marked loss of vision, had sudden diminution of vision with marked distortion and macular edema in his other eye. He responded dramatically to 1 week's administration of 3 mg. dexamethasone daily. Improvement was reflected in disappearance of distortion and edema and return of vision to 20/15. Treatment was continued at lower dosage for an additional 2 weeks. A similar improvement (from 20/80 to 20/30) was obtained in the only seeing eye of a highly myopic patient who had a loss of vision extending through 3 months, and had previously been given up as hopeless. It is assumed that macular edema was absorbed in both cases. Since the underlying pathology is not influenced, the possibility of a future relapse cannot be ruled out. Three other cases with macular changes and edema failed to respond to several weeks of dexamethasone therapy.

A case of herpes zoster with keratitis and severe uveitis responded dramatically to dexamethasone in initial doses of 3 mg. daily. Systemic treatment was continued for only 3 weeks. Topical dexamethasone was applied to the eye and skin concomitantly and after cessation of systemic therapy.

A female patient with a quiescent chronic uveitis, who developed a wide-angle glaucoma that required filtering surgery, was managed successfully with 3 mg. dexamethasone, daily during the treatment.

Three patients with central serous retinopathy were treated with dexamethasone. Duration of therapy was 7 months in one, and 4 months in another. One of these patients had an excellent response, while the patient who had been under treatment for the longer period was only starting to respond at this writing. Because of the length of time involved, the question arises as to whether the response can be attributed to the therapy. The third patient failed to respond.

Two patients with disciform keratitis were treated successfully with dexamethasone. The initial dosage was 3 mg. daily. Topical dexamethasone was employed concomitantly.

Summary

Sixty-six patients with various corticosteroid-responsive ocular conditions were treated with dexamethasone. Average initial dosages ranged from 1.5 mg. to 3 mg. daily, and maintenance dosages were adjusted according to individual requirements.

Dexamethasone proved to have the highest milligram activity of any corticosteroid studied by us; effective dosages are approximately one tenth those of prednisone, prednisolone, and 6-methylprednisolone or triamcinolone, and one thirtieth those of cortisone.

The only side effects observed with dexamethasone in this series were edema in varying degrees and four cases of varying degrees of acne; this is particularly gratifying since, in ophthalmology, one is more apt to elicit side effects because of the prolonged treatment at high-dosage levels frequently required in chronic intraocular inflammations. There were no gastrointestinal ulcers or other significant gastrointestinal reactions; two patients complained of bloating.

Dexamethasone proved a highly effective corticosteroid in the great majority of cases. As would be true with any steroid, in some patients its effect was no greater than that of previous corticoids, while in others the change to dexamethasone resulted in dramatic improvement. While dexamethasone is not the ultimate adrenocorticosteroid, it certainly represents a major step ahead in ocular anti-inflammatory therapy.

A large group of patients with various external ocular conditions has been treated with topical forms of dexamethasone. Since the results obtained were similar to those generally seen with prednisone or prednisolone, the series is not discussed here.

Acknowledgment

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Concluding Discussion

Philip S. Hench (*University of Minnesota* (*Mayo Foundation*) *and Mayo Clinic*, *Rochester*, *Minn.*): Dameshek, I believe, said that he felt satisfied with some of the older hormones, and perhaps was not as excited about some of the new ones as he might be. Occasionally, I have felt the same way and yet there is no question that keen clinicians are constantly pointing out that a change from one corticosteroid to another frequently produces responses that cannot be imagined beforehand. Therefore, we must be grateful for the challenge arising from the new compounds, and we must investigate these various drugs.

SUMMARY OF MONOGRAPH

Joseph J. Bunim

National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md., and the Johns Hopkins University School of Medicine, Baltimore, Md.

The knowledge acquired during the past decade, briefly and only partially reviewed in this monograph, is a brilliant illustration of the productivity and scientific achievement that may accrue to medical research from an effective coordination of multiple scientific disciplines: organic chemistry, biochemistry, physiology, and clinical investigation.

This kind of collaborative effort is symbolized by the work of Kendall and Hench and their associates, who activated this decade's progress by their historic contribution. Much has been learned concerning the pathways of biosynthesis of the active corticosteroids in mammalian adrenal cortex, and remarkable advances have been made in the partial and total synthesis of cortisone, hydrocortisone, and a host of derivatives.

It has been demonstrated that the rate of corticoid biosynthesis is regulated by the concentration of reduced triphosphopyridine nucleotide (TPNH) in the adrenals and the rate of degradation or saturation of these corticoids by the concentration of TPNH in the liver. Moreover, the levels of enzymes involved in the production of enzymes or coenzymes in the liver may be regulated in turn by hormones such as thyroxin.

It has been established that a subtle relationship exists between the molecular configuration of a corticosteroid and its anabolic, gluconeogenic, and electrolyte activities; its capacity to regulate corticotropin secretion; and its ability to suppress both experimental and clinical inflammation. It has been found that, in some instances, a single alteration in the structure of the naturally occurring corticosteroid may enhance one of its activities and at the same time markedly reduce another; in other instances, the introduction of multiple structural alterations may have additive or even synergistic effects.

The rate of biosynthesis of hydrocortisone in man has been measured, as has its distribution in body fluid, the rate of its disappearance from the circulation, and the renal excretion of its metabolites. The effects of hormonal imbalance, such as hyper- or hypothyroidism, and of hepatic dysfunction on the above physiological activities have been determined quantitatively.

The number of diseases in which the corticosteroids have been found useful, life-prolonging, or life-saving has increased far beyond the three originally reported by Hench and his associates: rheumatoid arthritis, rheumatic fever, and systemic lupus erythematosus. Now included are certain diseases of the eye, skin, kidneys, lungs, heart, blood, blood vessels, gastrointestinal tract, connective tissue, and muscle. In general, the corticosteroids have been found to be effective in suppressing reactions of inflammation and hypersensitivity.

In diseases such as nephrosis, the reported limitations of steroid therapy were later found to reflect only our own limited knowledge and skill in the administration of these agents for, with increased experience and competence, results of therapy in nephrosis are now often remarkable.

In diseases such as tuberculous meningitis and advanced pulmonary tuberculosis, where the corticosteroids were originally considered to be absolutely contraindicated, it was subsequently found that they prolonged or saved life when administered in combination with appropriate antibiotics.

During the past decade we have witnessed an advance of the greatest magnitude in the therapy of certain disabling, crippling, and fatal diseases whose etiology and pathogenesis are as yet unknown. There remain, however, serious limitations and hazards of steroid therapy that have not been overcome and that, consequently, continue to confront the physician with challenging problems in management. As the result of alteration in the molecular structure of the corticosteroids, of more judicious selection of suitable patients, and of more conservative dosage, some adverse effects have been significantly reduced in incidence or severity, but have not been eliminated.

Many patients who received long-term corticosteroid administration could not tolerate its discontinuance, while others could not tolerate its continuance, and many who responded dramatically initially derived little benefit when steroid therapy was prolonged.

Finally, the mechanism of action of these remarkable hormones still eludes us and, in so doing, gives direction to future research. It has been postulated[1] that, since the steroid molecule consists of a lipid nucleus and superimposed centers of unsaturation and oxygen functions, it would be oriented at a lipid-water interface such as the cell membrane. In this strategic position corticosteroids could govern intracellular biochemical activity by regulating the ingress and egress of key metabolites. The same influence could be effected at other phase boundaries within the cell structure. This hypothesis seems reasonable, since it is known that plasma protein binds these steroids and thus could carry them from the adrenal cortex to the peripheral cells, where they may complex with the intracellular nucleotide coenzymes and thus regulate the rate of enzymatic reaction.

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